

## ► INTRODUCTION

Relax.

This section is intended to make your exam preparation easier, not harder. Our goal is to reduce your level of stress and help you make the most of your study effort by helping you understand more about the United States Medical Licensing Examination, Step 1 (USMLE Step 1)—especially what the new FRED computer-based testing (CBT) is likely to mean to you. As a medical student, you are no doubt familiar with taking standardized examinations and quickly absorbing large amounts of material. When you first confront the USMLE Step 1, however, you may find it easy to become sidetracked and not achieve your goal of studying with maximum effectiveness. Common mistakes that students make when studying for the boards include the following:

- “Stressing out” owing to an inadequate understanding of the computer-based format
- Not understanding how scoring is performed or what your score means
- Starting *First Aid* too late
- Starting to study too late
- Using inefficient or inappropriate study methods
- Buying the wrong books or buying more books than you can ever use
- Buying only one publisher’s review series for all subjects
- Not using practice examinations to maximum benefit
- Not using review books along with your classes
- Not analyzing and improving your test-taking strategies
- Getting bogged down by reviewing difficult topics excessively
- Studying material that is rarely tested on the USMLE Step 1
- Failing to master certain high-yield subjects owing to overconfidence
- Using *First Aid* as your sole study resource

In this section, we offer advice to help you avoid these pitfalls and be more productive in your studies. To begin, it is important for you to understand what the examination involves.



*The USMLE assesses a physician’s ability to apply knowledge, concepts, and principles that are important in health and disease and that constitute the basis of safe and effective patient care.<sup>2</sup>*

## ► USMLE STEP 1—THE CBT BASICS

Some degree of concern about your performance on the USMLE Step 1 examination is both expected and appropriate. All too often, however, medical students become unnecessarily anxious about the examination. It is therefore important to understand precisely what the USMLE Step 1 involves. As you become familiar with Step 1, you can translate your anxiety into more efficient preparation.

The USMLE Step 1 is the first of three examinations that you must pass in order to become a licensed physician in the United States.<sup>1</sup> The USMLE is a joint endeavor of the National Board of Medical Examiners (NBME) and the

Federation of State Medical Boards (FSMB). In previous years, the examination was strictly organized around seven traditional disciplines: anatomy, behavioral science, biochemistry, microbiology, pathology, pharmacology, and physiology. In June 1991, the NBME began administering the “new” NBME Part I examination, which offered a more integrated and multidisciplinary format coupled with more clinically oriented questions.

In 1992, the USMLE replaced both the Federation Licensing Examination (FLEX) and the certifying examinations of the NBME.<sup>3</sup> The USMLE now serves as the single examination system for U.S. medical students and international medical graduates (IMGs) seeking medical licensure in the United States.

### How Is the CBT Structured?

The CBT Step 1 exam consists of seven question “blocks” of 50 questions each (see Figure 1) for a total of 350 questions, timed at 60 minutes per block. A short 11-question survey follows the last question block. The computer begins the survey with a prompt to proceed to the next block of questions. Don’t be fooled! “Block 8” is the NBME survey.

These blocks were designed to reduce eyestrain and fatigue during the exam. Once an examinee finishes a particular block, he or she must click on a screen icon to continue to the next block. Examinees will **not** be able to go back and change answers to questions from any previously completed block. Changing answers, however, is allowed **within** a block of questions as long as time permits.

Prometric test centers offer Step 1 on a year-round basis, except for the first two weeks in January. The exam is given every day except Sunday at most centers. Some schools administer the exam on their own campuses.

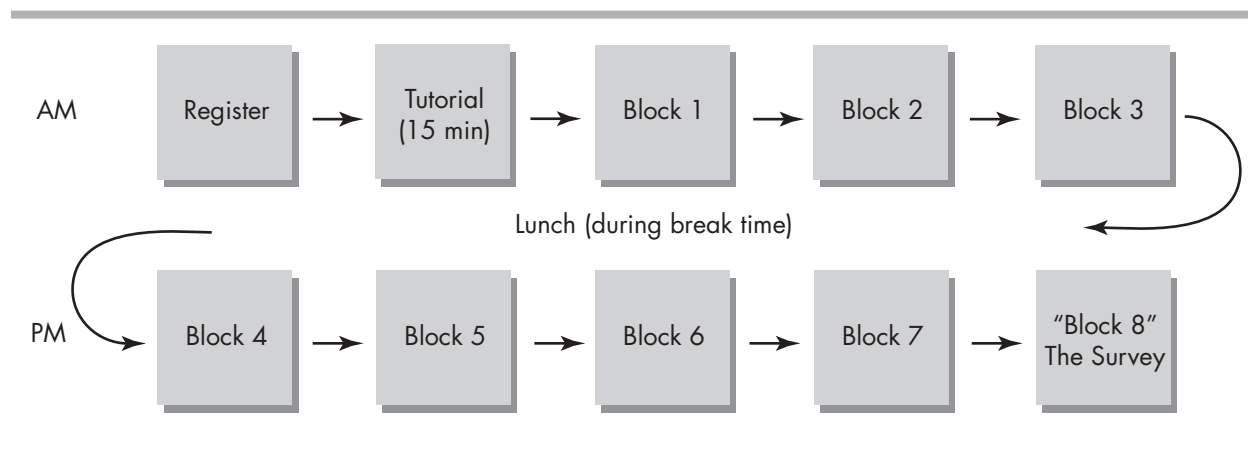


*The CBT format of Step 1 is simply a computerized version of the former paper exam.*



*Don’t be fooled! After the last question block comes the NBME survey (“Block 8”).*

FIGURE 1. Schematic of CBT Exam.





*Skip the tutorial and add 15 minutes to your break time!*

## What Is the CBT Like?

Because of the unique environment of the CBT, it's important that you be familiar ahead of time with what your test-day conditions will be like. Familiarizing yourself with the testing interface before the exam can add 15 minutes to your break time! This is because a 15-minute tutorial, offered on exam day, may be skipped if you are already familiar with the exam procedures and the testing interface (see description of CD-ROM below). The 15 minutes is added to your allotted break time (should you choose to skip the tutorial).

For security reasons, examinees are not allowed to bring any personal electronic equipment into the testing area. This includes digital watches, watches with computer communication and/or memory capability, cellular telephones, and electronic paging devices. Food and beverages are also prohibited. The testing centers are monitored by audio and video surveillance equipment.

In 2006, the USMLE completed its transition to FRED. FRED is a computer-based format that is similar to the old forms of CBT, with minor differences.



*Test illustrations include:*

- Gross photos
- Histology slides
- Radiographs
- EMs
- Line drawings

The typical question screen in FRED has a question followed by a number of choices on which an examinee can click, together with a number of navigational buttons on top. There is a countdown timer on the upper left-hand corner of the screen as well. There is also a button that allows the examinee to mark the question for review. If questions happen to be longer than the screen (which occurs very rarely), a scroll bar appears on the right, allowing the examinee to see the rest of the question. Regardless of whether the examinee clicks on the answer or leaves it blank, he or she must click the "Next" button to advance to the next question.

Some questions contain figures or color illustrations. These are typically situated to the right of the question. Although the contrast and brightness of the screen can be adjusted, there are no other ways to manipulate the picture (e.g., no zooming or panning).

The examinee can call up a window displaying normal lab values. In order to do so, he or she must hit the "Lab" icon on the top part of the screen. Afterward, the examinee will have the option to choose between "Blood," "Cerebrospinal," "Hematologic," or "Sweat and Urine." The normal-values screen may obscure the question if it is expanded. The examinee may have to scroll down to search for the needed laboratory values.

FRED allows the examinee to see a running list of the questions on the left part of the screen at all times. Also, with the new software, examinees will be able to highlight or cross out information using their mouse. Finally, there is an "Annotate" icon on the top part of the screen that allows students to write notes to themselves for review at a later time. Examinees need to be careful with all of these new features, because failure to do so can cost valuable time!

## What Does the CBT Format Mean to Me?

The significance of the CBT to you depends on the requirements of your school and your level of computer knowledge. If you hate computers and freak out whenever you see one, you might want to face your fears as soon as possible. Spend some time playing with a Windows-based system and pointing and clicking icons or buttons with a mouse. These are the absolute basics, and you won't want to waste valuable exam time figuring them out on test day. Your test taking will proceed by pointing and clicking, essentially without the use of the keyboard. The free CD is an excellent way to become familiar with the test interface.

For those who feel they would benefit, the USMLE offers an opportunity to take a simulated test, or "CBT Practice Session at a Prometric center." Students are eligible to take the three-and-one-half-hour practice session after they have received their fluorescent orange scheduling permit (see below).

The same USMLE Step 1 sample test items (150 questions) available on the CD or USMLE Web site, [www.usmle.org](http://www.usmle.org), are used at these sessions. **No new items will be presented.** The session is divided into three one-hour blocks of 50 test items each and costs about \$42. The student receives a printed percent-correct score after completing the session. No explanations of questions are provided.

You may register for a practice session online at [www.usmle.org](http://www.usmle.org).

## How Do I Register to Take the Exam?

Step 1 or Step 2 applications may be printed from the USMLE Web site. The application allows applicants to select one of 12 overlapping three-month blocks in which to be tested (e.g., April–May–June, June–July–August). The application includes a photo ID form that must be certified by an official at your medical school to verify your enrollment. After the NBME processes your application, it will send you a fluorescent orange slip of paper called a scheduling permit.

The scheduling permit you receive from the NBME will contain your USMLE identification number, the eligibility period in which you may take the exam, and two unique numbers. One of these is known as your "scheduling number." You must have this number to make your exam appointment with Prometric. The other number is known as the "candidate identification number," or CIN. Examinees must enter their CINs at the Prometric workstation to access their exams. Prometric has no access to the codes. **Do not lose your permit!** You will not be allowed to take the boards unless you present this permit along with an unexpired, government-issued photo identification with your signature (such as a driver's license or passport). Make sure the name on your photo ID exactly matches the name appearing on your scheduling permit.

Once you receive your scheduling permit, you may call the Prometric toll-free number to arrange a time to take the exam. Although requests for taking



### Keyboard shortcuts:

*A–E—Letter choices.*

*Enter or spacebar—Move to next question.*

*Esc—Exit pop-up Lab and Exhibit windows.*

*Alt-T—Countdown timers for current session and overall test.*



*Ctrl-Alt-Delete are the keys of death during the exam. Don't touch them!*



*Test scheduling is on a "first-come, first-served" basis. It's important to call and schedule an exam date as soon as you receive your scheduling permit.*





*Testing centers are closed on major holidays and during the first two weeks of January.*

the exam may be completed more than six months before the test date, examinees will not receive their scheduling permits earlier than six months before the eligibility period. The eligibility period is the three-month period you have chosen to take the exam. Most medical students choose the April–June or June–August period. Because exams are scheduled on a “first-come, first-served” basis, it is recommended that you telephone Prometric as soon as you have received your permit. After you’ve scheduled your exam, it’s a good idea to confirm your exam appointment with Prometric at least one week prior to your test date. Prometric does not provide written confirmation of exam date, time, or location. Be sure to read the *2007 USMLE Bulletin of Information* for further details.



*Register six months in advance for seating and scheduling preference.*

### **What If I Need to Reschedule the Exam?**

You can change your date and/or center by contacting Prometric at 1-800-MED-EXAM (1-800-633-3926) or [www.prometric.com](http://www.prometric.com). Make sure to have your CIN when rescheduling. If you are rescheduling by phone, you must speak with a Prometric representative; leaving a voice-mail message will not suffice. To avoid a rescheduling fee, you will need to request a change before noon EST at least five business days before your appointment. Please note that your rescheduled test date must fall within your assigned three-month eligibility period.

### **When Should I Register for the Exam?**

Although there are no deadlines for registering for Step 1, you should plan to register at least six months ahead of your desired test date. This will guarantee that you will get either your test center of choice or one within a 50-mile radius of your first choice. For most U.S. medical students, the desired testing window is in June, since most medical school curricula for the second year end in May or June. Thus, U.S. medical students should plan to register before January for a June test date. The timing of the exam is more flexible for IMGs, as it is related only to when they finish exam preparation.

Choose your three-month eligibility period wisely. If you need to reschedule outside your initial three-month period, you must submit a new application along with another application fee.

### **Where Can I Take the Exam?**

Your testing location is arranged with Prometric when you call for your test date (after you receive your scheduling permit). For a list of Prometric locations nearest you, visit [www.prometric.com](http://www.prometric.com).

## How Long Will I Have to Wait Before I Get My Scores?

The USMLE reports scores three to six weeks after the examinee's test date. Scores are always released on a Wednesday. During peak times, score reports may take up to six weeks. Official information concerning the time required for score reporting is posted on the USMLE Web site.

## What About Time?

Time is of special interest on the CBT exam. Here's a breakdown of the exam schedule:

15 minutes	Tutorial (skip if familiar)
7 hours	60-minute question blocks
45 minutes	Break time (includes time for lunch)

The computer will keep track of how much time has elapsed. However, the computer will show you only how much time you have remaining in a given block. Therefore, it is up to you to determine if you are pacing yourself properly (at a rate of approximately one question per 72 seconds).

The computer will **not** warn you if you are spending more than your allotted time for a break. You should therefore budget your time so that you can take a short break when you need it and have time to eat. You must be especially careful not to spend too much time in between blocks (you should keep track of how much time elapses from when you finish a block of questions to when you start the next block). After you finish one question block, you'll need to click the mouse when you are ready to proceed to the next block of questions.

Forty-five minutes is the minimum break time for the day. You can gain extra break time (but not time for the question blocks) by skipping the tutorial or by finishing a block ahead of the allotted time.

## If I Freak Out and Leave, What Happens to My Score?

Your scheduling permit shows a CIN that you will enter onto your computer screen to start your exam. Entering the CIN is the same as breaking the seal on a test book, and you are considered to have started the exam when you do so. However, no score will be reported if you do not complete the exam. In fact, if you leave at any time from the start of the test to the last block, no score will be reported. The fact that you started but did not complete the exam, however, will appear on your USMLE score transcript.

The exam ends when all blocks have been completed or their time has expired. As you leave the testing center, you will receive a printed test-completion notice to document your completion of the exam. To receive an official score, you must finish the entire exam.



*Be careful to watch the clock on your break time.*



*Gain extra break time by skipping the tutorial or finishing a block early.*



*Nearly three-fourths of Step 1 questions begin with a description of a patient.*

## What Types of Questions Are Asked?

Although numerous changes had to be made for the CBT format, the question types are the same as in previous years.

**One-best-answer items** are the only multiple-choice format. Most questions consist of a clinical scenario or a direct question followed by a list of five or more options. You are required to select the one best answer among the options. There are no “except,” “not,” or matching questions on the exam. A number of options may be partially correct, in which case you must select the option that best answers the question or completes the statement. Additionally, keep in mind that experimental questions may appear on the exam (see *Difficult Questions*, p. 23).

## How Is the Test Scored?

Each Step 1 examinee receives a score report that has the examinee’s pass/fail status, two test scores, and a graphic depiction of the examinee’s performance by discipline and organ system or subject area (see Figures 2A and 2B). The actual organ system profiles reported may depend on the statistical characteristics of a given administration of the examination.



*The mean Step 1 score for U.S. medical students rose from 200 in 1991 to 215 in 2000.*

For 1999, the NBME provided two overall test scores based on the total number of items answered correctly on the examination (see Figure 3). The first score, the three-digit score, was reported as a scaled score in which the mean was 215 and the standard deviation was 20. The second score scale, the two-digit score, defines 75 as the minimum passing score (equivalent to a score of 179 on the first scale). A score of 82 is equivalent to a score of 200 on the first score scale. To avoid confusion, we refer to scores using the three-digit scale with a mean of 215 and a standard deviation of 20.

A score of 182 or higher is required to pass Step 1. Passing the CBT Step 1 is estimated to correspond to answering 60–70% of questions correctly. In 2005, the pass rates for first-time test takers from accredited U.S. and Canadian medical schools was 90% (see Table 1). These statistics prove it—you’re much more likely to pass than fail. Although the NBME may adjust the minimum passing score at any time, no further adjustment is expected for several years.

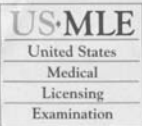


*Passing the CBT Step 1 is estimated to correspond to answering 60–70% of the questions correctly.*

According to the USMLE, medical schools receive a listing of total scores and pass/fail results plus group summaries by discipline and organ system. Students can withhold their scores from their medical school if they wish. Official USMLE transcripts, which can be sent on request to residency programs, include only total scores, not performance profiles.

Consult the USMLE Web site or your medical school for the most current and accurate information regarding the examination.

FIGURE 2A. Sample Score Report—Front Page.

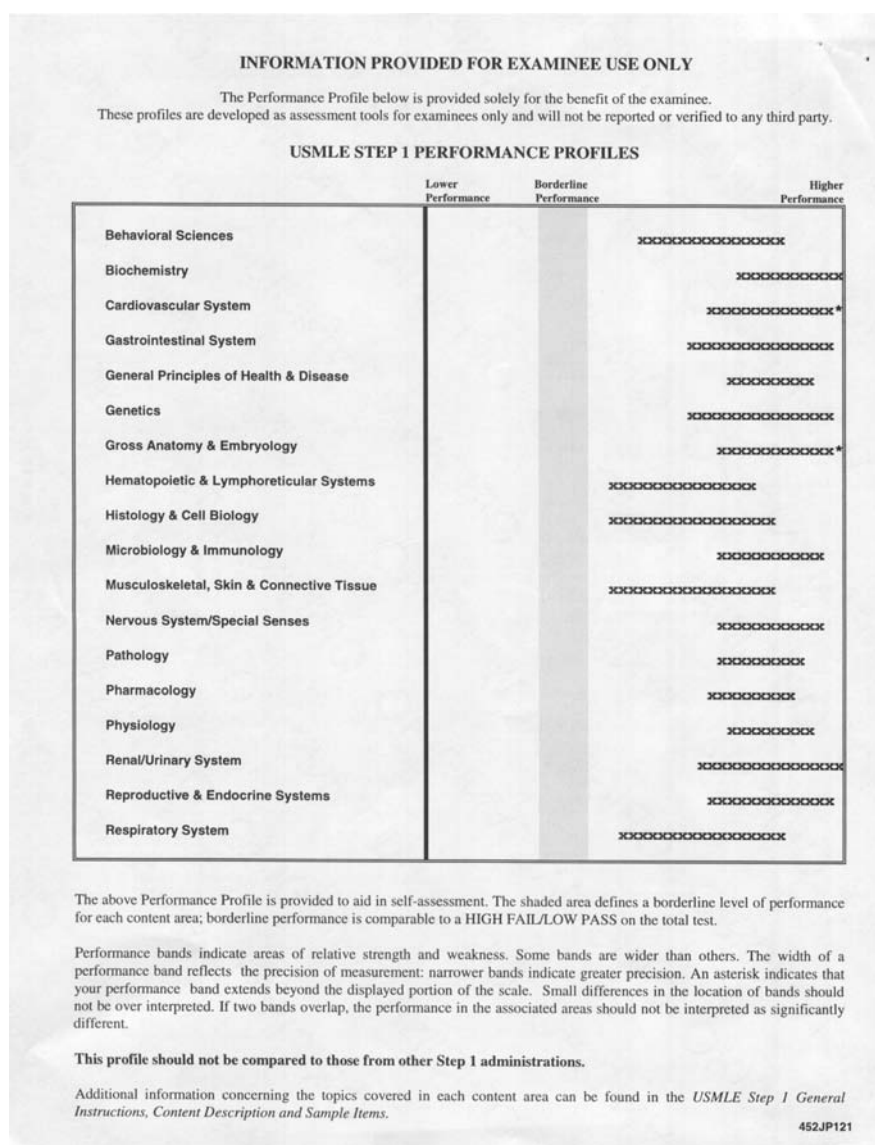
	<b>UNITED STATES MEDICAL LICENSING EXAMINATION™</b> USMLE Step 1 is administered to students and graduates of U.S. and Canadian medical schools by the <b>NATIONAL BOARD OF MEDICAL EXAMINERS® (NBME®)</b> 3750 Market Street, Philadelphia, Pennsylvania 19104-3190. Telephone: (215) 590-9700		
<b>STEP 1 SCORE REPORT</b>			
<table border="1" style="width: 100%;"> <tr> <td style="width: 50%;"> <b>Schmoe, Joe T</b>  <b>Anytown, CA 12345</b> </td> <td style="width: 50%;"> <b>USMLE ID: 1-234-567-8</b>  <b>Test Date: June 2002</b> </td> </tr> </table>		<b>Schmoe, Joe T</b> <b>Anytown, CA 12345</b>	<b>USMLE ID: 1-234-567-8</b> <b>Test Date: June 2002</b>
<b>Schmoe, Joe T</b> <b>Anytown, CA 12345</b>	<b>USMLE ID: 1-234-567-8</b> <b>Test Date: June 2002</b>		
<p>The USMLE is a single examination program for all applicants for medical licensure in the United States; it replaces the Federation Licensing Examination (FLEX) and the certifying examinations of the National Board of Medical Examiners (NBME Parts I, II and III). The program consists of three Steps designed to assess an examinee's understanding of and ability to apply concepts and principles that are important in health and disease and that constitute the basis of safe and effective patient care. Step 1 is designed to assess whether an examinee understands and can apply key concepts of the basic biomedical sciences, with an emphasis on principles and mechanisms of health, disease and modes of therapy. The inclusion of <b>Step 1</b> in the USMLE sequence is intended to ensure mastery of not only the basic medical sciences undergirding the safe and competent practice of medicine in the present, but also the scientific principles required for maintenance of competence through lifelong learning. Results of the examination are reported to medical licensing authorities in the United States and its territories for use in granting an initial license to practice medicine. The two numeric scores shown below are equivalent; each state or territory may use either score in making licensing decisions. These scores represent your results for the administration of Step 1 on the test date shown above.</p>			
<b>PASS</b>	This result is based on the minimum passing score set by USMLE for Step 1. Individual licensing authorities may accept the USMLE-recommended pass/fail result or may establish a different passing score for their own jurisdictions.		
<b>215</b>	This score is determined by your overall performance on Step 1. For recent administrations, the mean and standard deviation for first-time examinees from U.S. and Canadian medical schools are approximately 215 and 20, respectively, with most scores falling between 175 and 255. A score of 179 is set by USMLE to pass Step 1. The standard error of measurement (SEM) <sup>‡</sup> for this scale is four points.		
<b>85</b>	This score is also determined by your overall performance on the examination. A score of 82 on this scale is equivalent to a score of 200 on the scale described above. A score of 75 on this scale, which is equivalent to a score of 182 on the scale described above, is set by USMLE to pass Step 1. The SEM <sup>‡</sup> for this scale is one point.		
<p><sup>‡</sup>Your score is influenced both by your general understanding of the basic biomedical sciences and the specific set of items selected for this Step 1 examination. The SEM provides an estimate of the range within which your scores might be expected to vary by chance if you were tested repeatedly using similar tests.</p>			
121JP452			
NOTE: Original score report has copy-resistant watermark.			

### What Does My Score Mean?

For students, the most important point with the Step 1 score is passing versus failing. Passing essentially means, “Hey, you’re on your way to becoming a fully licensed doc.”

Beyond that, the main point of having a quantitative score is to give you a sense of how you’ve done aside from the fact that you’ve passed the exam. The two-digit or three-digit score gauges how you have done with respect to the content on the exam.

Since the content of the exam is what drives the score, the profile of the exam is what remains relatively constant over the years. That is to say that each exam pro-

**FIGURE 2B. Sample Score Report—Back Page.**

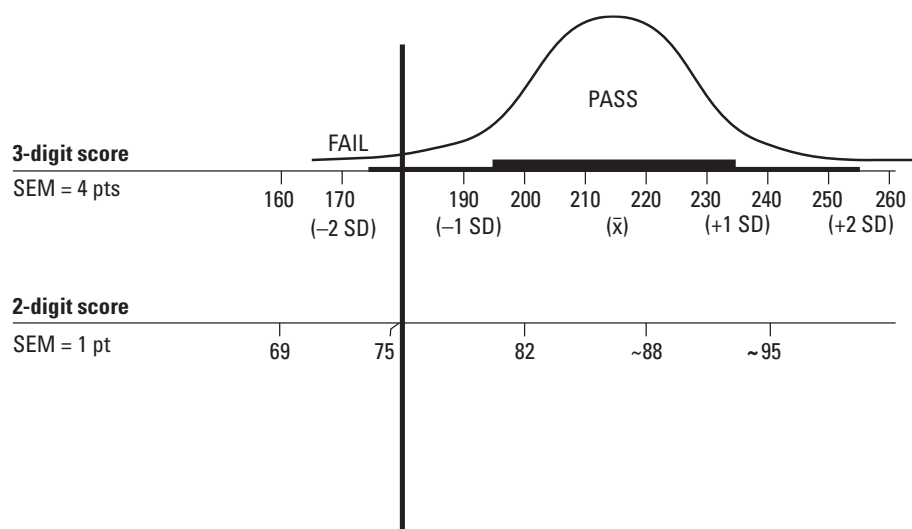
file includes a certain number of “very hard” questions along with “medium” and “easy” ones. The questions vary, but the profile of the exam doesn’t change much. This ensures that someone who scored 200 on the boards yesterday achieved a level of knowledge similar to that of the person who scored 200 four years ago.



*Practice questions may be easier than the actual exam.*

### Official NBME/USMLE Resources

We strongly encourage students to use the free materials provided by the testing agencies (see p. 25) and to study in detail the following NBME publications, all of which are available on CD-ROM or at the USMLE Web site, [www.usmle.org](http://www.usmle.org):

**FIGURE 3. Scoring Scales for the USMLE Step 1.****TABLE 1. Passing Rates for the 2004–2005 USMLE Step 1.<sup>a</sup>**

	<b>2004</b>		<b>2005</b>	
	<b>No. TESTED</b>	<b>PASSING (%)</b>	<b>No. TESTED</b>	<b>PASSING (%)</b>
NBME-registered examinees (U.S./Canadian)				
Allopathic students				
First-time takers	16,703	93	16,799	94
Repeaters	1,652	64	1,491	65
<b>Allopathic total</b>	<b>18,355</b>	<b>91</b>	<b>18,290</b>	<b>92</b>
Osteopathic students				
First-time takers	1,131	70	1,265	73
Repeaters	61	53	66	53
<b>Osteopathic total</b>	<b>1,192</b>	<b>69</b>	<b>1,331</b>	<b>72</b>
<b>Total (U.S./Canadian)</b>	<b>19,547</b>	<b>89</b>	<b>19,621</b>	<b>90</b>
IMG examinees (ECFMG <sup>b</sup> registrants)				
First-time takers	12,251	67	13,488	68
Repeaters	5,964	40	5,911	39
<b>IMG total</b>	<b>18,215</b>	<b>58</b>	<b>19,399</b>	<b>59</b>
<b>Total Step 1 examinees</b>	<b>37,762</b>	<b>74</b>	<b>39,020</b>	<b>75</b>

<sup>a</sup>Reflects the most current data available at the time of publishing.<sup>b</sup>Educational Commission for Foreign Medical Graduates.

- *USMLE Step 1 2007 Computer-based Content and Sample Test Questions* (information given free to all examinees)
- *2007 USMLE Bulletin of Information* (information given free to all examinees)
- Comprehensive Basic Science Self-Assessment (CBSSA)

The *USMLE Step 1 2007 Computer-based Content and Sample Test Questions* contains approximately 150 questions that are similar in format and content to the questions on the actual USMLE Step 1. This practice test offers one of the best methods for assessing your test-taking skills. However, it does not contain enough questions to simulate the full length of the examination, and its content represents a limited sampling of the basic science material that may be covered on Step 1. Most students felt that the questions on the actual 2005 exam were more challenging than those contained in these sample questions. Others report encountering a few near-duplicates of these questions on the actual Step 1. Presumably, these are “experimental” questions, but who knows! Bottom line: Know these questions!

The extremely detailed *Step 1 Content Outline* provided by the USMLE has not proved useful for students studying for the exam. The USMLE even states that “. . . the content outline is not intended as a guide for curriculum development or as a study guide.”<sup>4</sup> We concur with this assessment.

The *2007 USMLE Bulletin of Information* is found on the CD-ROM. This publication contains detailed procedural and policy information regarding the CBT, including descriptions of all three Steps, scoring of the exams, reporting of scores to medical schools and residency programs, procedures for score rechecks and other inquiries, policies for irregular behavior, and test dates.

The NBME also offers the Comprehensive Basic Science Self-Assessment (CBSSA), which tests users on topics covered during basic science courses in a format similar to that of the USMLE Step 1 examination. The Web-based information provided via the CBSSA is intended for use as a study tool and not as an indicator of Step 1 performance. However, students who prepared for the examination using this Web-based tool found the format and content highly indicative of questions tested for the Step 1 examination.

The CBSSA exists in two forms: a standard-paced and a self-paced format, both of which consist of four sections of 50 questions each (a total of 400 multiple-choice items). The standard-paced format allows the user up to one hour to complete each section, reflecting the time limits of the actual exam. The self-paced format, however, places no time limit on answering the multiple-choice questions. Keep in mind that this bank of questions is available only on the Web. The NBME requires that users log on, register, and start within 30 days of registration. Once the assessment has begun, users are required to complete the sections within 20 days. Upon completion of the questions, the CBSSA will provide the user with a performance profile, indicating relative strengths and weaknesses, similar to the report profile for the USMLE Step 1 exam. However, please keep in mind that this self-assessment does not provide the user with a list of correct answers. Feedback from the self-assessment is entirely in the format of a performance profile and nothing more. The NBME charges \$45 for this ser-



vice, which is payable by credit card or money order. For more information regarding the CBSSA, please visit the NBME's Web site at [www.nbme.org](http://www.nbme.org) and click on the link for "NBME Web-based Self-Assessment Service."

### ► DEFINING YOUR GOAL

It is useful to define your own personal performance goal when approaching the USMLE Step 1. Your style and intensity of preparation can then be matched to your goal. Your goal may depend on your school's requirements, your specialty choice, your grades to date, and your personal assessment of the test's importance. Do your best to define your goals early so that you can prepare accordingly.

Certain highly competitive residency programs, such as those in otolaryngology and orthopedic surgery, have acknowledged their use of Step 1 scores in the selection process. In such residency programs, greater emphasis may be placed on attaining a high score, so students who seek to enter these programs may wish to consider aiming for a very high score on the USMLE Step 1. However, a great number of residency programs value other criteria more highly than a high score on Step 1. For more information, fourth-year medical students who have recently completed the residency application process can be a valuable resource.



*Fourth-year medical students have the best feel for how Step 1 scores factor into the residency application process.*



*Some competitive residency programs use Step 1 scores in their selection process.*

### ► TIMELINE FOR STUDY

#### **Make a Schedule**

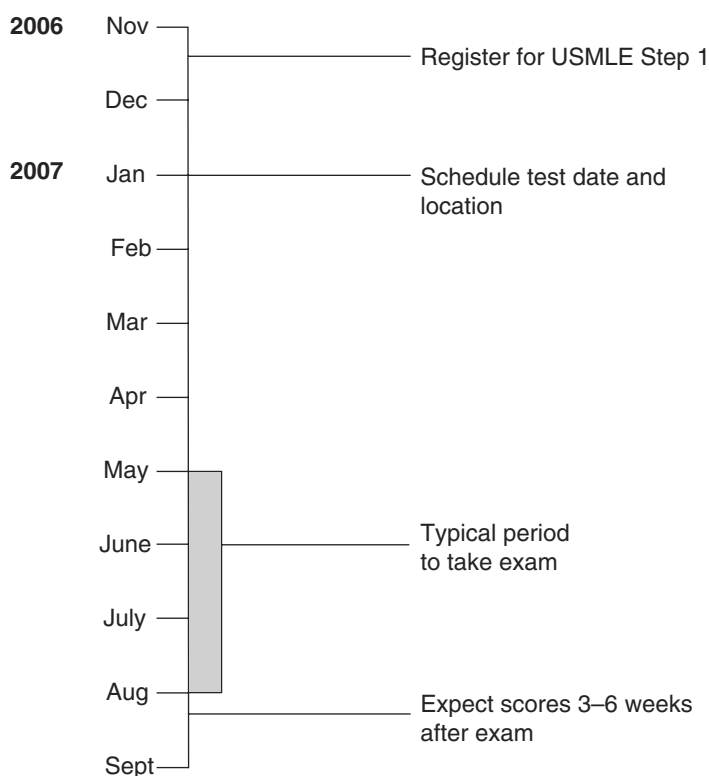
After you have defined your goals, map out a study schedule that is consistent with your objectives, your vacation time, and the difficulty of your ongoing coursework (see Figure 4). Determine whether you want to spread out your study time or concentrate it into 14-hour study days in the final weeks. Then factor in your own history in preparing for standardized examinations (e.g., SAT, MCAT).

Typically, students allot between five and seven weeks to prepare for Step 1. Some students reserve about a week at the end of their study period for final review; others save just a few days. When you have scheduled your exam date, do your best to keep to it. Recent studies show that a later testing date does not translate into a higher score, so avoid pushing back your test date.<sup>5</sup> This highlights the importance of working out a realistic schedule to which you can adhere.

Another important consideration is when you will study each subject. Some subjects lend themselves to cramming, whereas others demand a substantial long-term commitment. The "crammable" subjects for Step 1 are those for which concise yet relatively complete review books are available. (See Section IV for highly rated review and sample examination materials.) Behavioral sci-



*Time management is key. Customize your schedule to your goals and available time following any final exams.*

**FIGURE 4. Typical Timeline for the USMLE Step 1.**

*“Crammable” subjects should be covered later and less crammable subjects earlier.*

ence and physiology are two subjects with concise review books. Three subjects with longer but quite complete review books are microbiology, pharmacology, and biochemistry. Thus, these subjects could be covered toward the end of your schedule, whereas other subjects (anatomy and pathology) require a longer time commitment and could be studied earlier. Many students prefer using a “systems-based” approach (e.g., GI, renal, cardiovascular) to integrate the material across basic science subjects. See Section III to study anatomy, pathology, physiology, and pharmacology facts by organ system.

Practically speaking, spending a given amount of time on a crammable or high-yield subject (particularly in the last few days before the test) generally produces more correct answers on the examination than spending the same amount of time on a low-yield subject. Student opinion indicates that knowing the crammable subjects extremely well probably results in a higher overall score than knowing all subjects moderately well.

Make your schedule realistic, and set achievable goals. Many students make the mistake of studying at a level of detail that requires too much time for a comprehensive review—reading *Gray’s Anatomy* in a couple of days is not a realistic goal! Revise your schedule regularly on the basis of your actual progress. Be careful not to lose focus. Beware of feelings of inadequacy when comparing study schedules and progress with your peers. **Avoid students who stress you out.** Fo-

cus on a few top-rated resources that suit your learning style—not on some obscure books your friends may pass down to you. Do not set yourself up for frustration. Accept the fact that you cannot learn it all. Maintain your sanity throughout the process.

You will need time for uninterrupted and focused study. Plan your personal affairs to minimize crisis situations near the date of the test. Allot an adequate number of breaks in your study schedule to avoid burnout. Maintain a healthy lifestyle with proper diet, exercise, and sleep.

### **Year(s) Prior**

The NBME asserts that the best preparation for the USMLE Step 1 resides in “broadly based learning that establishes a strong general foundation of understanding of concepts and principles in basic sciences.”<sup>6</sup> We agree. Although you may be tempted to rely solely on cramming in the weeks and months before the test, you should not have to do so. The knowledge you gained during your first two years of medical school and even during your undergraduate years should provide the groundwork on which to base your test preparation. Student scores on NBME subject tests (commonly known as “shelf exams”) have been shown to be highly correlated with subsequent Step 1 scores.<sup>7</sup> Moreover, undergraduate science GPAs as well as MCAT scores are strong predictors of performance on the Step 1 exam.<sup>8</sup> The preponderance of your boards preparation should thus involve resurrecting dormant information that you have stored away during the basic science years.

We also recommend that you buy highly rated review books early in your first year of medical school and use them as you study throughout the two years. When Step 1 comes along, the books will be familiar and personalized to the way in which you learn. It is risky and intimidating to use unfamiliar review books in the final two or three weeks.

### **Months Prior**

Review test dates and the application procedure. In 2007, the testing for the USMLE Step 1 continues on a year-round basis (see Table 2). If you have any disabilities or “special circumstances,” contact the NBME as early as possible to discuss test accommodations (see p. 56, First Aid for the Student with a Disability).

Before you begin to study earnestly, simulate the USMLE Step 1 under “real” conditions to pinpoint strengths and weaknesses in your knowledge and test-taking skills. Be sure that you are well informed about the examination and that you have planned your strategy for studying. Consider what study methods you will use, the study materials you will need, and how you will obtain your materials. Plan ahead. Get advice from third- and fourth-year medical students who have recently taken the USMLE Step 1. There might be strengths and weaknesses in your school’s curriculum that you should take into account in decid-



*Avoid burnout. Maintain proper diet, exercise, and sleep habits.*



*Buy review books early (first year) and use while studying for courses.*



*Simulate the USMLE Step 1 under “real” conditions before beginning your studies.*

TABLE 2. 2007 USMLE Exams.

STEP	Focus	No. of Questions/ No. of Blocks	TEST SCHEDULE LENGTH OF CBT EXAM	PASSING SCORE
Step 1	Basic mechanisms and principles	350/7	One day (eight hours)	182
Step 2	Clinical diagnosis and disease pathogenesis	400/8	One day (nine hours)	174
Step 3	Clinical management	500/10	Two days (16 hours)	182

ing where to focus your efforts. You might also choose to share books, notes, and study hints with classmates. That is how this book began.



*In the final two weeks, focus  
on review and endurance.  
Avoid unfamiliar material.  
Stay confident!*

### Three Weeks Prior

Two to four weeks before the examination is a good time to resimulate the USMLE Step 1. You may want to do this earlier depending on the progress of your review, but do not do it later, when there will be little time to remedy defects in your knowledge or test-taking skills. Make use of remaining good-quality sample USMLE test questions, and try to simulate the computerized test conditions so that you get a fair assessment of your test performance. Recognize, too, that time pressure is increasing as more and more questions are framed as clinical vignettes. Most sample exam questions are shorter than the real thing. Focus on reviewing the high-yield facts, your own notes, picture books, and very short review books.



*Confirm your testing date at  
least one week in advance.*

### One Week Prior

Make sure you have your CIN (found on your scheduling permit) and other items necessary for the day of the examination, including a driver's license or other photo identification with your signature (make sure the name on your ID **exactly** matches that on your scheduling permit), an analog watch, and possibly earplugs. Confirm the Prometric testing center location and test time. Work out how you will get to the testing center and what parking and traffic problems you might encounter. Visit the testing site (if possible) to get a better idea of the testing conditions. Determine what you will do for lunch. Make sure you have everything you need to ensure that you will be comfortable and alert at the test site.

### One Day Prior

Try your best to relax and rest the night before the test. Double-check your admissions and test-taking materials as well as the comfort measures discussed earlier so that you do not have to deal with such details on the morning of the

exam. Do not study any new material. If you feel compelled to study, then quickly review short-term-memory material (e.g., Rapid Review) before going to sleep. However, do not quiz yourself, as you may risk becoming flustered and confused. Remember that regardless of how hard you studied, you cannot know everything. There will be things on the exam that you have never even seen before, so do not panic. Do not underestimate your abilities.

Many students report difficulty sleeping the night prior to the exam. This is often exacerbated by going to bed much earlier than usual. Do whatever it takes to ensure a good night's sleep (e.g., massage, exercise, warm milk). Do not change your daily routine prior to the exam. Exam day is not the day for a caffeine-withdrawal headache.

### Morning of the Exam

Wake up at your regular time and eat a normal breakfast. Make sure you have your scheduling permit admission ticket, test-taking materials, and comfort measures as discussed earlier. Wear loose, comfortable clothing. Plan for a variable temperature in the testing center. Arrive at the test site 30 minutes before the time designated on the admission ticket; however, do not come too early, as this may increase your anxiety. When you arrive at the test site, the proctor should give you a blue, laminated USMLE information sheet to read that will explain important things such as the use of break time. Seating may be assigned, but ask to be reseated if necessary; you need to be seated in an area that will allow you to remain comfortable and to concentrate. Get to know your testing station, especially if you have never been in a Prometric testing center before. Listen to your proctors regarding any changes in instructions or testing procedures that may apply to your test site.

Remember that it is natural (and even beneficial) to be a little nervous. Focus on being mentally clear and alert. Avoid panic. Avoid panic. Avoid panic. When you are asked to begin the exam, take a deep breath, focus on the screen, and then begin. Keep an eye on the timer. Take advantage of breaks between blocks to stretch and relax for a moment.

### After the Test

Have fun and relax regardless of how you may feel. Taking the test is an achievement in itself. Remember, you are much more likely to have passed than not. Enjoy the free time you have before your clerkships. Expect to experience some “reentry” phenomena as you try to regain a real life. Once you have recovered sufficiently from the test (or from partying), we invite you to send us your feedback, corrections, and suggestions for entries, facts, mnemonics, strategies, resource ratings, and the like (see p. xv, How to Contribute). Sharing your experience benefits fellow medical students and IMGs.



*No notes, books, calculators, pagers, recording devices, or digital watches are allowed in the testing area.*



*Arrive at the testing center 30 minutes before your scheduled exam time. If you arrive more than half an hour late, you will not be allowed to take the test.*



*Some students recommend reviewing certain “theme” topics that tend to recur throughout the exam.*



*If you pass Step 1, you are not allowed to retake the exam in an attempt to raise your score.*

**TABLE 3. Pass Rates for USMLE Step 1 Repeaters 1999.<sup>9</sup>**

INITIAL SCORE	% PASS
176–178	83
173–175	74
170–172	71
165–169	64
160–164	54
150–159	31
< 150	0
<b>Overall</b>	<b>67</b>

### ► IF YOU THINK YOU FAILED

After the test, many examinees feel that they have failed, and most are at the very least unsure of their pass/fail status. There are several sensible steps you can take to plan for the future in the event that you do not achieve a passing score. First, save and organize all your study materials, including review books, practice tests, and notes. Familiarize yourself with the reapplication procedures for Step 1, including application deadlines and upcoming test dates. The CBT format allows an examinee who has failed the exam to retake it no earlier than the first day of the month after 60 days have elapsed since the last test date. Examinees will, however, be allowed to take the exam no more than three times within a 12-month period should they repeatedly fail.

The performance profiles on the back of the USMLE Step 1 score report provide valuable feedback concerning your relative strengths and weaknesses (see Figure 2B). Study the performance profiles closely. Set up a study timeline to strengthen gaps in your knowledge as well as to maintain and improve what you already know. Do not neglect high-yield subjects. It is normal to feel somewhat anxious about retaking the test. If anxiety becomes a problem, however, seek appropriate counseling.

Fifty-two percent of the NBME-registered first-time takers who failed the June 1998 Step 1 repeated the exam in October 1998. The overall pass rate for that group in October was 60%. Eighty-five percent of those scoring near the old pass/fail mark of 176 (173–176) in June 1998 passed in October. However, 1999 pass rates varied widely depending on initial score (see Table 3, which reflects the most current data available at the time of publishing).

Although the NBME allows an unlimited number of attempts to pass Step 1, both the NBME and the FSMB recommend that licensing authorities allow a minimum of three and a maximum of six attempts for each Step examination.<sup>9</sup> Again, review your school's policy regarding retakes.

### ► IF YOU FAILED

Even if you came out of the exam room feeling that you failed, seeing that failing grade can be traumatic, and it is natural to feel upset. Different people react in different ways: For some it is a stimulus to buckle down and study harder; for others it may “take the wind out of their sails” for a few days; and for still others it may lead to a reassessment of individual goals and abilities. In some instances, however, failure may trigger weeks or months of sadness, feelings of hopelessness, social withdrawal, and inability to concentrate—in other words, true clinical depression. If you think you are depressed, please seek help.

## ► STUDY METHODS

It is important to have a set of study methods for preparing for the USMLE Step 1. There is too much material to justify a studying plan that is built on random reading and memorization. Experiment with different ways of studying. You do not know how effective something might be until you try it. This is best done months before the test to determine what works and what you enjoy. Possible study options include the following:

- Studying review material in groups
- Creating personal mnemonics, diagrams, and tables
- Using *First Aid* as a framework on which to add notes
- Taking practice computer as well as pencil-and-paper tests (see Section IV for “resources”)
- Attending faculty review sessions
- Making or sharing flash cards
- Reviewing old syllabi and notes
- Making cassette tapes of review material to study during commuting time
- Playing Trivial Pursuit–style games with facts and questions
- Getting away from home for an extended period to avoid distractions and to immerse yourself in studying

### Study Groups

A good study group has many advantages. It can relieve stress, organize your time, and allow people with different strengths to exchange information. Study groups also allow you to pool resources and spend less money on review books and sample tests.

There are, however, potential problems associated with study groups. Above all, it is difficult to study with people who have different goals and study paces. Avoid study groups that tend to socialize more than study. If you choose not to belong to a study group, it may be a good idea to find a support group or a study partner with whom to keep pace and share study ideas. It is beneficial to get different perspectives from other students.

### Mnemonics and Memorizing

Mnemonics are memory aids that work by linking isolated facts or abstract ideas to acronyms, pictures, patterns, rhymes, and stories—information that the mind tends to store well.<sup>11</sup> The best mnemonics are your own, and developing them takes work. The first step to creating a mnemonic is understanding the information to be memorized. Play around with the information and look for unique features that help you remember it. Effective mnemonics should link the topic with the facts in as specific and unambiguous a manner as possible. Keep the information fresh by quizzing yourself periodically with flash cards, in study groups, and so on. Do not make the common mistake of simply



*Near the failure threshold, each three-digit scale point is equivalent to about 1.5 questions answered correctly.<sup>10</sup>*



*Balance individual and group study.*



*Developing good mnemonics takes time and work. Quiz yourself periodically. Do not simply reread highlighted material.*



rereading highlighted review material. The material may start to look familiar, but that does not mean you will be able to remember it in another context during the exam. Strive to gain an understanding rather than rote memorization.

### Review Sessions

Faculty review sessions can also be helpful. Review sessions that are geared specifically toward the USMLE Step 1 tend to be more helpful than general review sessions. By contrast, open “question and answer” sessions tend to be inefficient and not worth the time. Focus on reviews given by faculty who are knowledgeable in the content and testing format of the USMLE Step 1.

### Commercial Courses

Commercial preparation courses can be helpful for some students, but they are expensive and require significant time commitment. The data also show that such courses have a limited impact on Step 1 scores.<sup>12</sup> However, this may reflect the fact that students who take such courses are concerned about their readiness to take the exam. Nevertheless, commercial courses are often an effective organizing tool for students who feel overwhelmed by the sheer volume of material involved in preparing for Step 1. Note, however, that multiple-week courses may be quite intense and may thus leave limited time for independent study.

## ► STUDY MATERIALS

### Quality and Cost Considerations

Although an ever-increasing number of review books and software are now available on the market, the quality of such material is highly variable. Some common problems are as follows:

- Certain review books are too detailed for review in a reasonable amount of time or cover subtopics that are not emphasized on the exam.
- Many sample question books were originally written years ago and have not been adequately updated to reflect recent trends.
- Many sample question books use poorly written questions or contain factual errors in their explanations.
- Explanations for sample questions vary in quality.



*If a given review book is not working for you, stop using it no matter how highly rated it may be or how much it costs.*

### Basic Science Review Books

In selecting review books, be sure to weigh different opinions against each other, read the reviews and ratings in Section IV of this guide, examine the books closely in the bookstore, and choose carefully. You are investing not only money but also your limited study time. Do not worry about finding the “perfect” book, as many subjects simply do not have one, and different students prefer different styles.

There are two types of review books: books that are stand-alone titles and books that are part of a series. The books in a series generally have the same style, and you must decide if that style works for you. However, a given style is not optimal for every subject. For example, charts and diagrams may be the best approach for physiology and biochemistry, whereas tables and outlines may be preferable for microbiology.

You should also find out which books are up to date. Some new editions represent major improvements, whereas others contain only cursory changes. Take into consideration how a book reflects the format of the USMLE Step 1.

### Practice Tests

Taking practice tests provides valuable information about potential strengths and weaknesses in your fund of knowledge and test-taking skills. Some students use practice examinations simply as a means of breaking up the monotony of studying and adding variety to their study schedule, whereas other students study almost solely from practice tests. Your best preview of the computerized exam can be found in the practice exams on the USMLE CD-ROM. Some students also recommend using computerized test simulation programs. In addition, students report that many current practice-exam books have questions that are, on average, shorter and less clinically oriented than the current USMLE Step 1.

After taking a practice test, try to identify concepts and areas of weakness, not just the facts that you missed. Do not panic if you miss a lot of questions on a practice examination; instead, use the experience you have gained to motivate your study and prioritize those areas in which you need the most work. Use quality practice examinations to improve your test-taking skills. Analyze your ability to pace yourself.

### Clinical Review Books

Keep your eye out for more clinically oriented review books; purchase them early and begin to use them. A number of students are turning to Step 2 books, pathophysiology books, and case-based reviews to prepare for the clinical vignettes. Examples of such books include:

- *First Aid for the® Wards* (McGraw-Hill)
- *First Aid Clerkship* series (McGraw-Hill)
- *Blueprints* clinical series (Blackwell Science)
- *PreTest Physical Diagnosis* (McGraw-Hill)
- *Washington Manual* (Lippincott Williams & Wilkins)
- Various USMLE Step 2 review books



*Most practice exams are shorter and less clinical than the real thing.*



*Use practice tests to identify concepts and areas of weakness, not just facts that you missed.*

## Texts, Syllabi, and Notes

Limit your use of texts and syllabi for Step 1 review. Many textbooks are too detailed for high-yield review and include material that is generally not tested on the USMLE Step 1 (e.g., drug dosages, complex chemical structures). Syllabi, although familiar, are inconsistent and frequently reflect the emphasis of individual faculty, which often does not correspond to that of the USMLE Step 1. Syllabi also tend to be less organized and to contain fewer diagrams and study questions than do top-rated review books.

### ► GENERAL STUDY STRATEGIES



*Familiarize yourself with the commonly tested normal laboratory values.*



*Practice questions that include case histories or descriptive vignettes are critical for Step 1 preparation.*



*Practice and perfect test-taking skills and strategies well before the test date.*

The USMLE Step 1 was created according to an integrated outline that organizes basic science material in a multidisciplinary approach. Broad-based knowledge is now more important than it was in the exams of prior years. The exam is designed to test basic science material and its application to clinical situations. Approximately three-quarters of the questions include clinical vignettes, although some are brief. Some useful studying guidelines are as follows:

- Be familiar with the CBT tutorial. This will give you 15 minutes of extra break time.
- Use computerized practice tests in addition to paper exams.
- Consider doing a simulated test at a Prometric center.
- Practice taking 50 questions in one-hour bursts.
- Be familiar with the Windows environment.
- Consider scheduling a light rotation for your first clinical block in case you get a test date later than you expected.

Practice questions that include case histories or descriptive vignettes are critical in preparing for the clinical slant of the USMLE Step 1. The normal lab values provided on the computerized test are difficult to use and access. For quick reference, see the table of high-yield laboratory values on the inside back cover of this book.

### ► TEST-TAKING STRATEGIES

Your test performance will be influenced by both your fund of knowledge and your test-taking skills. You can increase your performance by considering each of these factors. Test-taking skills and strategies should be developed and perfected well in advance of the test date so that you can concentrate on the test itself. We suggest that you try the following strategies to see if they might work for you.

## Pacing

You have seven hours to complete 350 questions. Note that each one-hour block contains 50 questions. This works out to about 72 seconds per question.

NBME officials note that time was not an issue for most takers of the CBT field test. However, pacing errors have in the past been detrimental to the performance of even highly prepared examinees. The bottom line is to keep one eye on the clock at all times!

### Dealing with Each Question

There are several established techniques for efficiently approaching multiple-choice questions; see what works for you. One technique begins with identifying each question as easy, workable, or impossible. Your goal should be to answer all easy questions, work out all workable questions in a reasonable amount of time, and make quick and intelligent guesses on all impossible questions. Most students read the stem, think of the answer, and turn immediately to the choices. A second technique is to first skim the answer choices and the last sentence of the question and then read through the passage quickly, extracting only relevant information to answer the question. Try a variety of techniques on practice exams and see what works best for you.

### Difficult Questions

Because of the exam's clinical emphasis, you may find that many of the questions appear workable but take more time than is available to you. It can be tempting to dwell on such questions for an excessive amount of time because you feel you are on the verge of "figuring it out," but resist this temptation and budget your time. Answer difficult questions with your best guess, mark them for review, and come back to them if you have time after you have completed the rest of the questions in the block. This will keep you from inadvertently leaving any questions blank in your efforts to "beat the clock."

Another reason for not dwelling too long on any one question is that certain questions may be **experimental** or may be **incorrectly phrased**. Moreover, not all questions are scored. Some questions serve as "embedded pretest items" that do not count toward your overall score.<sup>11</sup> In fact, anywhere from 10% to 20% of exam questions have been designated as experimental on past exams.

### Guessing

There is **no penalty** for wrong answers. Thus, no test block should be left with unanswered questions. A hunch is probably better than a random guess. If you have to guess, we suggest selecting an answer you recognize over one that is totally unfamiliar to you.

### Changing Your Answer

The conventional wisdom is not to change answers that you have already marked unless there is a convincing and logical reason to do so—in other



*Time management is an important skill for exam success.*



*Do not dwell excessively on questions that you are on the verge of "figuring out." Make your best guess and move on.*



*Remember that some questions may be experimental.*



*Your first hunch is not always correct.*



*Do not terminate the block too early. Carefully review your answers if possible.*



*Be prepared to read fast and think on your feet!*



*Step 1 vignettes usually describe diseases or disorders in their most classic presentation.*

words, go with your “first hunch.” However, studies show that if you change your answer, you are twice as likely to change it from an incorrect answer to a correct one than vice versa. So if you have a strong “second hunch,” go for it!

#### **Fourth-Quarter Effect (Avoiding Burnout)**

Pacing and endurance are important. Practice helps develop both. Fewer and fewer examinees are leaving the examination session early. Use any extra time you might have at the end of each block to return to marked questions or to recheck your answers; you cannot add the extra time to any remaining blocks of questions or to your break time. Do not be too casual in your review or you may overlook serious mistakes. Remember your goals, and keep in mind the effort you have devoted to studying compared with the small additional effort you will need to maintain focus and concentration throughout the examination. Never give up. If you begin to feel frustrated, try taking a 30-second breather.

#### **► CLINICAL VIGNETTE STRATEGIES**

In recent years, the USMLE Step 1 has become increasingly clinically oriented. Students polled from 2003 exams report that nearly 80% of the questions were presented as clinical vignettes. This change mirrors the trend in medical education toward introducing students to clinical problem solving during the basic science years. The increasing clinical emphasis on Step 1 may be challenging to those students who attend schools with a more traditional curriculum.

#### **What Is a Clinical Vignette?**

A clinical vignette is a short (usually paragraph-long) description of a patient, including demographics, presenting symptoms, signs, and other information concerning the patient. Sometimes this paragraph is followed by a brief listing of important physical findings and/or laboratory results. The task of assimilating all this information and answering the associated question in the span of one minute can be intimidating. Be prepared to read fast and think on your feet. Remember that the question is often indirectly asking something you already know.

#### **Strategy**

Remember that the Step 1 vignettes usually describe diseases or disorders in their most classic presentation. Look for buzzwords or cardinal signs (e.g., malar rash for SLE or nuchal rigidity for meningitis) in the narrative history. Be aware, however, that the question may contain classic signs and symptoms instead of mere buzzwords. Sometimes the data from labs and the physical exam will help you confirm or reject possible diagnoses, thereby helping you rule answer choices in or out. In some cases, they will be a dead giveaway for the diagnosis.

Making a diagnosis from the history and data is often not the final answer. Not infrequently, the diagnosis is divulged at the end of the vignette, after you have just struggled through the narrative to come up with a diagnosis of your own. The question might then ask about a related aspect of the diagnosed disease.



*Sometimes making a diagnosis is not necessary at all.*

One strategy that many students suggest is to skim the questions and answer choices before reading a vignette, especially if the vignette is lengthy. This focuses your attention on the relevant information and reduces the time spent on that vignette. Sometimes you may not need much of the information in the vignette to answer the question.

#### ► TESTING AGENCIES

##### **National Board of Medical Examiners (NBME)**

Department of Licensing Examination Services  
3750 Market Street  
Philadelphia, PA 19104-3102  
(215) 590-9700  
Fax: (215) 590-9457  
E-mail: [webmail@nbme.org](mailto:webmail@nbme.org)  
[www.nbme.org](http://www.nbme.org)

##### **Educational Commission for Foreign Medical Graduates (ECFMG)**

3624 Market Street, Fourth Floor  
Philadelphia, PA 19104-2685  
(215) 386-5900  
Toll free within North America: (800) 500-8249  
Fax: (215) 386-9196  
E-mail: [info@ecfm.org](mailto:info@ecfm.org)  
[www.ecfm.org](http://www.ecfm.org)

##### **Federation of State Medical Boards (FSMB)**

P.O. Box 619850  
Dallas, TX 75261-9850  
(817) 868-4000  
Fax: (817) 868-4099  
E-mail: [usmle@fsm.org](mailto:usmle@fsm.org)  
[www.fsm.org](http://www.fsm.org)

##### **USMLE Secretariat**

3750 Market Street  
Philadelphia, PA 19104-3190  
(215) 590-9700  
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[www.usmle.org](http://www.usmle.org)

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## ► FIRST AID FOR THE INTERNATIONAL MEDICAL GRADUATE

“International medical graduate” (IMG) is the term now used to describe any student or graduate of a non-U.S., non-Canadian, non-Puerto Rican medical school, regardless of whether he or she is a U.S. citizen. The old term “foreign medical graduate” (FMG) was replaced because it was misleading when applied to U.S. citizens attending medical schools outside the United States.

### The IMG’s Steps to Licensure in the United States

If you are an IMG, you must go through the following steps (not necessarily in this order) to become licensed to practice in the United States. You must complete these steps even if you are already a practicing physician and have completed a residency program in your own country.

- Complete the basic sciences program of your medical school (equivalent to the first two years of U.S. medical school).
- Take the USMLE Step 1. You can do this while still in school or after graduating, but in either case your medical school must certify that you completed the basic sciences part of your school’s curriculum before taking the USMLE Step 1.
- Complete the clinical clerkship program of your medical school (equivalent to the third and fourth years of U.S. medical school).
- Take the USMLE Step 2 Clinical Knowledge (CK) exam. If you are still in medical school, you must have completed two years of school.
- Take the Step 2 Clinical Skills (CS) exam.
- Graduate with your medical degree.
- Then, send the ECFMG a copy of your degree and transcript, which they will verify with your medical school.
- Obtain an ECFMG certificate. To do this, candidates must accomplish the following:
  - Graduate from a medical school that is listed in the International Medical Education Directory (IMED). The list can be accessed at [www.ecfmg.org](http://www.ecfmg.org).
  - Pass Step 1, the Step 2 CK, and the Step 2 CS within a seven-year period.
  - Have their medical credentials verified by the ECFMG.
- The standard certificate is usually sent two weeks after all the above requirements have been fulfilled. You must have a valid certificate before entering an accredited residency program, although you may begin the application process before you receive your certification.
- Apply for residency positions in your field of interest, either directly or through the Electronic Residency Application Service (ERAS) and the National Residency Matching Program (“the Match”). To be entered into the Match, you need to have passed all the examinations necessary for ECFMG certification (i.e., Step 1, the Step 2 CK, and the Step 2 CS) by the rank order list deadline (February 21, 2007, for the 2007 Match). If you do not pass these exams by the deadline, you will be withdrawn from the Match.



*More detailed information can be found in the 2007 edition of the ECFMG Information Booklet, available at [www.ecfmg.org/pubshome.html](http://www.ecfmg.org/pubshome.html).*



*Applicants may apply online for the USMLE Step 2 CK or Step 2 CS or request an extension of the USMLE eligibility period at [www.ecfmg.org/usmle/index.html](http://www.ecfmg.org/usmle/index.html) or [www.ecfmg.org/usmle/step2cs/index.html](http://www.ecfmg.org/usmle/step2cs/index.html).*

- Obtain a visa that will allow you to enter and work in the United States if you are not already a U.S. citizen or a green-card holder (permanent resident).
- If required for IMGs by the state in which your residency is located, obtain an educational/training/limited medical license. Your residency program may assist you with this application. Note that medical licensing is the prerogative of each individual state, not of the federal government, and that states vary with respect to their laws about licensing (although all 50 states recognize the USMLE).
- In order to begin your residency program, make sure your scores are valid.
- Once you have the ECFMG certification, take the USMLE Step 3 during your residency, and then obtain a full medical license. Once you have a license in any state, you are permitted to practice in federal institutions such as VA hospitals and Indian Health Service facilities in any state. This can open the door to “moonlighting” opportunities and possibilities for an H1B visa application. For details on individual state rules, write to the licensing board in the state in question or contact the FSMB.
- Complete your residency and then take the appropriate specialty board exams in order to become board certified (e.g., in internal medicine or surgery). If you already have a specialty certification in your home country (e.g., in surgery or cardiology), some specialty boards may grant you six months’ or one year’s credit toward your total residency time.
- Currently, many residency programs are accepting applications through ERAS. For more information, see *First Aid for the Match* or contact:

**ECFMG/ERAS Program**

P.O. Box 11746

Philadelphia, PA 19101-0746

(215) 386-5900

Fax: (215) 222-5641

e-mail: [eras-support@ecfm.org](mailto:eras-support@ecfm.org)

[www.ecfm.org/eras](http://www.ecfm.org/eras)

## **The USMLE and the IMG**

The USMLE is a series of standardized exams that give IMGs a level playing field. It is the same exam series taken by U.S. graduates even though it is administered by the ECFMG rather than by the NBME. This means that passing marks for IMGs for Step 1, the Step 2 CK, and the Step 2 CS are determined by a statistical process that is based on the scores of U.S. medical students. For example, to pass Step 1, you will probably have to score higher than the bottom 8–10% of U.S. and Canadian graduates.

## **Timing of the USMLE**

For an IMG, the timing of a complete application is critical. It is extremely important that you send in your application early if you are to garner the maximum number of interview calls. A rough guide would be to complete all exam requirements by August of the year in which you wish to apply. This

would translate into sending both your score sheets and your ECFMG certificate with your application.

In terms of USMLE exam order, arguments can be made for taking the Step 1 or the Step 2 CK exam first. For example, you may consider taking the Step 2 CK exam first if you have just graduated from medical school and the clinical topics are still fresh in your mind. However, keep in mind that there is a large overlap between Step 1 and Step 2 CK topics in areas such as pharmacology, pathophysiology, and biostatistics. You might therefore consider taking the Step 1 and Step 2 CK exams close together to take advantage of this overlap in your test preparation.

### **USMLE Step 1 and the IMG**

**What Is the USMLE Step 1?** It is a computerized test of the basic medical sciences that consists of 350 multiple-choice questions divided into seven blocks.

**Content.** Step 1 includes test items in the following content areas:

- Anatomy
- Behavioral sciences
- Biochemistry
- Microbiology and immunology
- Pathology
- Pharmacology
- Physiology
- Interdisciplinary topics such as nutrition, genetics, and aging

**Significance of the Test.** Step 1 is required for the ECFMG certificate as well as for registration for the Step 2 CS. Since most U.S. graduates apply to residency with their Step 1 scores only, it may be the only objective tool available with which to compare IMGs with U.S. graduates.

**Official Web Sites.** [www.usmle.org](http://www.usmle.org) and [www.ecfm.org/usmle](http://www.ecfm.org/usmle).

**Eligibility.** Both students and graduates from medical schools that are listed in IMED are eligible to take the test. Students must have completed at least two years of medical school by the beginning of the eligibility period selected.

**Eligibility Period.** A three-month period of your choice.

**Fee.** The fee for Step 1 is \$685 plus an international test delivery surcharge (if you choose a testing region other than the United States or Canada).

**Retaking the Exam.** In the event that you failed the test, you can reapply and select an eligibility period that begins at least 60 days after the last attempt. You cannot take the same Step more than three times in any 12-month period. You cannot retake the exam if you passed. The minimum score to pass

the exam is 75 on a two-digit scale. To pass, you must answer roughly 60–65% of the questions correctly.

**Statistics.** In 2004, only 67% of ECFMG candidates passed Step 1 on their first attempt, compared with 93% of U.S. and Canadian medical students and graduates. Of note, 1994–1995 data showed that USFMGs (U.S. citizens attending non-U.S. medical schools) performed 0.4 SD lower than IMGs (non-U.S. citizens attending non-U.S. medical schools). Although their overall scores were lower, USFMGs performed better than IMGs on behavioral sciences. In general, students from non-U.S. medical schools perform worst in behavioral science and biochemistry (1.9 and 1.5 SDs below U.S. students) and comparatively better in gross anatomy and pathology (0.7 and 0.9 SD below U.S. students). Although derived from data collected in 1994–1995, these data may help you focus your studying efforts.

**Tips.** Although few if any students feel totally prepared to take Step 1, IMGs in particular require serious study and preparation to reach their full potential on this exam. It is also imperative that IMGs do their best on Step 1, as a poor score on Step 1 is a distinct disadvantage in applying for most residencies. Remember that if you pass Step 1, you cannot retake it in an attempt to improve your score. Your goal should thus be to beat the mean, because you can then confidently assert that you have done better than average for U.S. students. Good Step 1 scores will also lend credibility to your residency application and help you get into highly competitive specialties such as radiology, orthopedics, and dermatology.

**Commercial Review Courses.** Do commercial review courses help improve your scores? Reports vary, and such courses can be expensive. Many IMGs decide to try the USMLE on their own and then consider a review course only if they fail. Just keep in mind that many states require that you pass the USMLE within three attempts. (For more information on review courses, see Section IV.)

## USMLE Step 2 CK and the IMG

**What Is the Step 2 CK?** It is a computerized test of the clinical sciences consisting of 368 multiple-choice questions divided into eight blocks. It can be taken at Prometric centers in the United States and several other countries.

**Content.** The Step 2 CK includes test items in the following content areas:

- Internal medicine
- Obstetrics and gynecology
- Pediatrics
- Preventive medicine
- Psychiatry
- Surgery
- Other areas relevant to the provision of care under supervision

**Significance of the Test.** The Step 2 CK is required for the ECFMG certificate. It reflects the level of clinical knowledge of the applicant. It tests clinical subjects, primarily internal medicine. Other areas that are tested are surgery, obstetrics and gynecology, pediatrics, orthopedics, psychiatry, ENT, ophthalmology, and medical ethics.

**Official Web Sites.** [www.usmle.org](http://www.usmle.org) and [www.ecfm.org/usmle](http://www.ecfm.org/usmle).

**Eligibility.** Students and graduates from medical schools that are listed in IMED are eligible to take the Step 2 CK. Students must have completed at least two years of medical school. This means that students must have completed the basic medical science component of the medical school curriculum by the beginning of the eligibility period selected.

**Eligibility Period.** A three-month period of your choice.

**Fee.** The fee for the Step 2 CK is \$685 plus an international test delivery surcharge (if you choose a testing region other than the United States or Canada).

**Retaking the Exam.** In the event that you fail the Step 2 CK, you can reapply and select an eligibility period that begins at least 60 days after the last attempt. You cannot take the same Step more than three times in any 12-month period. You cannot retake the exam if you passed.

**Statistics.** In 2003–2004, 75% of ECFMG candidates passed Step 2 on their first attempt, compared with 92% of U.S. and Canadian candidates.

**Tips.** It's better to take the Step 2 CK after you have completed your internal medicine rotation because most of the questions give clinical scenarios and ask you to make medical diagnoses and clinical decisions. In addition, because this is a clinical sciences exam, cultural and geographic considerations play a greater role than is the case with Step 1. For example, if your medical education gave you ample exposure to malaria, brucellosis, and malnutrition but little to alcohol withdrawal, child abuse, and cholesterol screening, you must work to familiarize yourself with topics that are more heavily emphasized in U.S. medicine. You must also have a basic understanding of the legal and social aspects of U.S. medicine, because you will be asked questions about communicating with and advising patients.

### **USMLE Step 2 CS and the IMG**

**What Is the Step 2 CS?** The Step 2 CS is a test of clinical and communication skills administered as a one-day, eight-hour exam. It includes 10 to 12 encounters with standardized patients (15 minutes each, with 10 minutes to write a note after each encounter). Test results are valid indefinitely.

**Content.** The Step 2 CS tests the ability to communicate in English as well as interpersonal skills, data-gathering skills, the ability to perform a

physical exam, and the ability to formulate a brief note, a differential diagnosis, and a list of diagnostic tests. The areas that are covered in the exam are as follows:

- Internal medicine
- Surgery
- Obstetrics and gynecology
- Pediatrics
- Psychiatry
- Family medicine

Unlike the USMLE Step 1, Step 2 CK, or Step 3, there are no numerical grades for the Step 2 CS—it's simply either a "Pass" or "Fail." To pass, a candidate must attain a passing performance in **each** of the following three components:

- Integrated Clinical Encounter (ICE): includes Data Gathering, Physical Exam, and the Patient Note
- Spoken English Proficiency (SEP)
- Communication and Interpersonal Skills (CIS)

According to the NBME, the most common component failed by IMGs on the Step 2 CS is the CIS component.

**Significance of the Test.** The Step 2 CS is required for the ECFMG certificate. It has eliminated the Test of English as a Foreign Language (TOEFL) as a requirement for ECFMG certification.

**Official Web Site.** [www.ecfmg.org/usmle/step2cs](http://www.ecfmg.org/usmle/step2cs).

**Eligibility.** Students must have completed at least two years of medical school in order to take the test. That means students must have completed the basic medical science component of the medical school curriculum at the time they apply for the exam.

**Fee.** The fee for the Step 2 CS is \$1200.

**Scheduling.** You must schedule the Step 2 CS within **four months** of the date indicated on your notification of registration. You must take the exam within 12 months of the date indicated on your notification of registration. It is generally advisable to take the Step 2 CS as soon as possible in the year before your Match, as often the results either come in late or come too late to retake it and pass it before the Match.

**Retaking the Exam.** There is no limit to the number of attempts you can make to pass the Step 2 CS. However, you cannot retake the exam within 60 days of a failed attempt, and you cannot take it more than three times in a 12-month period.

**Test Site Locations.** The Step 2 CS is currently administered at the following five locations:

- Philadelphia, PA
- Atlanta, GA
- Los Angeles, CA
- Chicago, IL
- Houston, TX

For more information about the Step 2 CS exam, please refer to *First Aid for the Step 2 CS*.

### **USMLE Step 3 and the IMG**

**What Is the USMLE Step 3?** It is a two-day computerized test in clinical medicine consisting of 480 multiple-choice questions and nine computer-based case simulations (CCS). The exam aims at testing your knowledge and its application to patient care and clinical decision making (i.e., this exam tests if you can safely practice medicine independently and without supervision).

**Significance of the Test.** Taking Step 3 before residency is critical if an IMG is seeking an H1B visa and is a bonus that can be added to the residency application. Step 3 is also required to obtain a full medical license in the United States and can be taken during residency for this purpose.

**Official Web Site.** [www.usmle.org](http://www.usmle.org).

**Fee.** The fee for Step 3 is \$590 (the total application fee can vary among states).

**Eligibility.** Most states require that applicants have completed one, two, or three years of postgraduate training (residency) before they apply for Step 3 and permanent state licensure. The exceptions are the 13 states mentioned below, which allow IMGs to take Step 3 at the beginning of or even before residency. So if you don't fulfill the prerequisites to taking Step 3 in your state of choice, simply use the name of one of the 13 states in your Step 3 application. You can take the exam in any state you choose regardless of the state that you mentioned on your application. Once you pass Step 3, it will be recognized by all states. Basic eligibility requirements for the USMLE Step 3 are as follows:

- Obtaining an MD or DO degree (or its equivalent) by the application deadline.
- Obtaining an ECFMG certificate if you are a graduate of a foreign medical school or are successfully completing a "fifth pathway" program (at a date no later than the application deadline).
- Meeting the requirements imposed by the individual state licensing authority to which you are applying to take Step 3. Please refer to [www.fsmb.org](http://www.fsmb.org) for more information.



The following states do not have postgraduate training as an eligibility requirement to apply for Step 3:

- Arkansas
- California
- Connecticut
- Florida
- Louisiana
- Maryland
- Nebraska\*
- New York
- South Dakota
- Texas
- Utah\*
- Washington
- West Virginia

\* Requires that IMGs obtain a “valid indefinite” ECFMG certificate.

The Step 3 exam is not available outside the United States. Applications can be found online at [www.fsmb.org](http://www.fsmb.org) and must be submitted to the FSMB.

### **Residencies and the IMG**

It is becoming increasingly difficult for IMGs to obtain residencies in the United States given the rising concern about an oversupply of physicians in the United States. Official bodies such as the Council on Graduate Medical Education (COGME) have recommended that the total number of residency slots be reduced. Furthermore, changes in immigration law are likely to make it much harder for noncitizens or legal residents of the United States to remain in the country after completing a residency.

In the residency Match, the number of U.S.-citizen IMG applications has been stable for the past few years, while the percentage accepted has slowly increased. For non-U.S.-citizen IMGs, applications fell from 7977 in 1999 to 5554 in 2005, while the percentage accepted significantly increased (see Table 4). This decrease in the total number of IMGs applying for the Match may be attributed to several factors:

- A decrease in the Step 2 CS passing rate to 80%.
- Increased difficulty obtaining U.S. visas.
- Increased expenses associated with the USMLE exams, ERAS, and travel to the United States.
- An increase in the number of IMGs who are withdrawing from the Match to sign a separate “pre-Match” contract with programs.

More information about residency programs can be obtained at [www.ama-assn.org](http://www.ama-assn.org).

TABLE 4. IMGs in the Match.

APPLICANTS	2003	2004	2005
U.S.-citizen IMGs	1987	2015	2091
% U.S.-citizens IMGs accepted	55	55	55
Non-U.S.-citizen IMGs	5029	5671	5554
% non-U.S.-citizens IMGs accepted	56	52	56
U.S. graduates (non-IMGs)	14,332	14,609	14,719
% U.S. graduates accepted	93	93	94

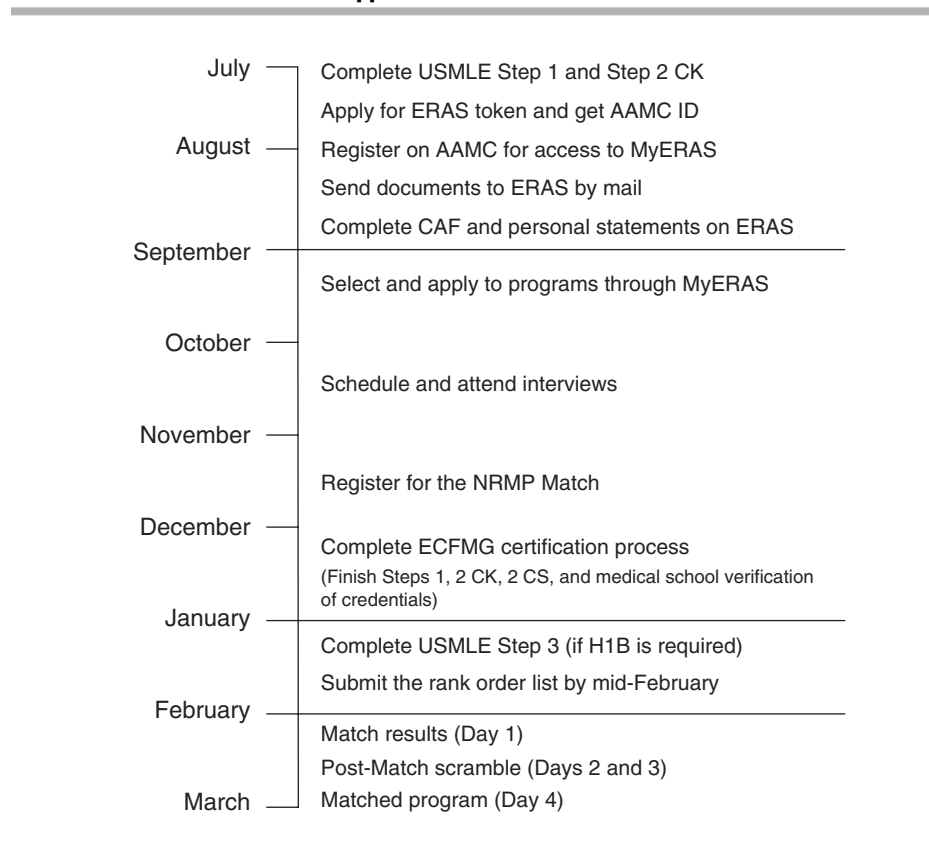
### The Match and the IMG

Due to an increased number of IMG candidates with strong applications, good USMLE scores are not the only way to gain a competitive edge. However, USMLE Step 1 and Step 2 CK scores continue to be used as the initial screen for considering candidates for interviews.

Based on accumulated IMG match experiences over the recent years, here are a few pointers to help IMGs to maximize chances for a residency interview.

### The IMG Checklist

- **Apply early.** Programs offer a limited number of interviews and often select candidates on a first come–first served basis. Because of this, aim to complete the entire process of applying for the ERAS token, registering with the Association of American Medical Colleges (AAMC), mailing necessary documents to ERAS, and completing the ERAS application before September (see Figure 5). Community programs usually send out interview offers earlier than university and university-affiliated programs.
- **U.S. clinical experience helps.** Externships and observerships in an American hospital setting have emerged as an important credential on an IMG application. Externships are like short-term medical school internships and offer hands-on clinical experience. Observerships, also called “shadowing,” involve following a physician and observing how he manages patients. Externships are considered superior to observerships, but having either of them is always better than having none. Some programs require students to have participated in an externship or observership before applying. It is best to get such an experience before or at the time of applying to programs, so you can mention it on your ERAS application. If such an experience or opportunity comes up after you apply, be sure to inform the programs.

**FIGURE 5. IMG Timeline for Application.**

- **Clinical research helps.** University programs are attracted to candidates who show a strong interest in clinical research and academics. They may even relax their application criteria for individuals with unique backgrounds and strong research experience. Publications in well-known journals are an added bonus.
- **Time the Step 2 CS well.** ECFMG has published the new Step 2 CS score reporting schedule for the years 2006–2007 at: <http://ecfmg.org/announce.htm#reportsched>. Most program directors would like to see a passing score on Step 1, Step 2 CK, and Step 2 CS before they rank an IMG on their rank order list in mid-February. There have been too many instances of candidates missing out on a position on the rank order list and thus a match, due to either delayed CS results or not being able to retake the exam on time after a failure. It is tough to predict a result on the Step 2 CS, since the grading process is not very transparent. Therefore, it is advisable to take the Step 2 CS as early as possible in the application year.
- **U.S. letters of recommendation (LORs) help.** LORs from clinicians practicing in the United States carry more weight than recommendations from home countries.
- **Step up the Step 3.** If H1B visa sponsorship is desired, aim to have Step 3 results by January of the Match year. Besides the visa advantage, an early

and good Step 3 score may benefit those IMGs who have been away from clinical medicine for a while and those who have low scores on Step 1 and Step 2 CK.

- **Verify medical credentials in a timely manner.** Do not overlook the medical school credentials verification process. The ECFMG certificate arrives only after credentials have been verified, in addition to passing Step 1, Step 2 CK, and, Step 2 CS, so it's good to keep track of the process and keep checking with ECFMG from time to time about the status.
- **Schedule interviews with prematches in mind.** Schedule interviews with your favorite programs first. This will leave you better prepared to make a decision in case you are offered a pre-Match position.

### Visa Options for the IMG

If you are living outside the United States, you will need to apply for a visa that will allow you lawful entry into the United States in order to take the Step 2 CS and/or do your interviews for residency. A B1 or B2 visitor visa may be issued by the U.S. consulate in your country. Citizens of some countries may have to undergo an additional security check that could take up to six months. Upon your entry into the United States, either the B1 or, more commonly, the B2 will be issued on your I-94. Both visas allow you a limited period within which to stay in the United States (two to six months) in order to take the exam. If the given period is not sufficient, you may apply for an extension before the expiration of your I-94.

Documents that are recommended to facilitate this process include the following:

- The Step 2 CS admission permit and a letter from the ECFMG (which explains why the applicant must enter the United States)
- Your medical diploma
- Transcripts from your medical school
- Your USMLE score sheets
- A sponsor letter or affidavit of support stating that you (if you are sponsoring yourself) or your sponsor will bear the expense of your trip and that you have sufficient funds to meet that expense
- An alien status affidavit

Individuals from certain countries may be allowed to enter the United States for up to 90 days without a visa under the Visa Waiver Program. See <http://uscis.gov>.

As an IMG, you need a visa to work or train in the United States unless you are a U.S. citizen or a permanent resident (i.e., hold a green card). Two types of visas enable you to accept a residency appointment in the United States: J1 and H1B. Most sponsoring residency programs (SRPs) prefer a J1 visa. Above all, this is because SRPs are authorized by the Department of Homeland Security (DHS) to issue a Form DS-2019 directly to an IMG. By contrast, SRPs must complete considerable paperwork, including an application to the Immigra-

tion and Labor Department, to apply to the DHS for an H1B visa on behalf of an IMG.

### The J1 Visa

Also known as the Exchange Visitor Program, the J1 visa was introduced to give IMGs in diverse specialties the chance to use their training experience in the United States to improve conditions in their home countries. As mentioned above, the DHS authorizes most SRPs to issue Form DS-2019 in the same manner that I-20s are issued to regular international students in the United States.

To enable an SRP to issue a DS-2019, you must obtain a certificate from the ECFMG indicating that you are eligible to participate in a residency program in the United States. First, however, you must ask the Ministry of Health in your country to issue a statement indicating that your country needs physicians with the skills you propose to acquire from a U.S. residency program. This statement, which must bear the seal of your country's government and must be signed by a duly designated government official, is intended to satisfy the U.S. Secretary of Health and Human Services (HHS) that there is such a need. The Health Ministry in your country should send this statement to the ECFMG (or they may allow you to mail it to the ECFMG).

How can you find out if the government of your country will issue such a statement? In many countries, the Ministry of Health maintains a list of medical specialties in which there is a need for further training abroad. You can also consult seniors in your medical school. A word of caution: If you are applying for a residency in internal medicine and internists are not in short supply in your country, it may help to indicate an intention to pursue a subspecialty after completing your residency training.

The text of your statement of need should read as follows:

Name of applicant for visa: \_\_\_\_\_. There currently exists in \_\_\_\_\_ (your country) a need for qualified medical practitioners in the specialty of \_\_\_\_\_. (Name of applicant for visa) has filed a written assurance with the government of this country that he/she will return to \_\_\_\_\_ (your country) upon completion of training in the United States and intends to enter the practice of medicine in the specialty for which training is being sought.

Stamp (or seal and signature) of issuing official of named country.  
Dated \_\_\_\_\_

To facilitate the issuing of such a statement by the Ministry of Health in your country, you should submit a certified copy of the agreement or a contract from your SRP in the United States. The agreement or contract must be signed by you and the residency program official responsible for the training.

Armed with Form DS-2019, you should then go to the U.S. consulate closest to the residential address indicated in your passport. As for other nonimmigrant visas, you must show that you have a genuine nonimmigrant intent to return to your home country. You must also show that all your expenses will be paid.

When you enter the United States, bring your Form DS-2019 along with your visa. You are usually admitted to the United States for the length of the J1 program, designated as “D/S,” or duration of status. The duration of your program is indicated on the DS-2019.

In the wake of the terrorist attacks of September 11, 2001, a number of new regulations have been introduced to improve the monitoring of exchange visitors during their time in the United States. All SRPs and students are currently required to register with the Student and Exchange Visitor Program (SEVP) via the Student and Exchange Visitor Information System (SEVIS). SEVIS allows the DHS to maintain up-to-date information (e.g., enrollment status, current address) on exchange visitors. SEVIS Form DS-2019 is used for visa applications, admission, and change of status. Procedural details for this new legislation are still being hammered out, so contact your SRP or check <http://uscis.gov> for the most current information.

**Duration of Participation.** The duration of a resident’s participation in a program of graduate medical education or training is limited to the time normally required to complete such a program. If you would like to get an idea of the typical training time for the various medical subspecialties, you may consult the *Directory of Medical Specialties*, published by Marquis Who’s Who for the American Board of Medical Specialties. The authority charged with determining the duration of time required by an individual IMG is the State Department. The maximum amount of time for participation in a training program is ordinarily limited to seven years unless the IMG has demonstrated to the satisfaction of the ECFMG and the State Department that his or her home country has an exceptional need for the specialty in which he or she will receive further training. An extension of stay may be granted in the event that an IMG needs to repeat a year of clinical medical training or needs time for training or education to take an exam required for board certification.

**Requirements after Entry into the United States.** Each year, all IMGs participating in a residency program on a J1 visa must furnish the Attorney General of the United States with an affidavit (Form I-644) attesting that they are in good standing in the program of graduate medical education or training in which they are participating and that they will return to their home countries upon completion of the education or training for which they came to the United States.

**Restrictions under the J1 Visa.** No later than two years after the date of entry into the United States, an IMG participating in a residency program on a J1

visa is allowed one opportunity to change his or her designated program of graduate medical education or training if his or her director approves that change.

The J1 visa includes a condition called the “two-year foreign residence requirement.” The relevant section of the Immigration and Nationality Act states:

Any exchange visitor physician coming to the United States on or after January 10, 1977, for the purpose of receiving graduate medical education or training is automatically subject to the two-year home-country physical presence requirement of section 212(e) of the Immigration and Nationality Act, as amended. Such physicians are not eligible to be considered for section 212(e) waivers on the basis of “No Objection” statements issued by their governments.

The law thus requires that a J1 visa holder, upon completion of the training program, leave the United States and reside in his or her home country for a period of at least two years. Currently, the American Medical Association (AMA) is advocating that this period be extended to five years.

An IMG on a J1 visa is ordinarily not allowed to change from a J1 to most other types of visas or (in most cases) to change from J1 to permanent residence while in the United States until he or she has fulfilled the “foreign residence requirement.” The purpose of the foreign residence requirement is to ensure that an IMG uses the training he or she obtained in the United States for the benefit of his or her home country. The U.S. government may, however, waive the two-year foreign residence requirement under the following circumstances:

- If you as an IMG can prove that returning to your country would result in “exceptional hardship” to you or to members of your immediate family who are U.S. citizens or permanent residents;
- If you as an IMG can demonstrate a “well-founded fear of persecution” due to race, religion, or political opinions if forced to return to your country;
- If you obtain a “no objection” statement from your government; or
- If you are sponsored by an “interested governmental agency” or a designated state Department of Health in the United States.

**Applying for a J1 Visa Waiver.** IMGs who have sought a waiver on the basis of the last alternative have found it beneficial to approach the following potentially “interested government agencies”:

- **The Department of Health and Human Services.** Recently, HHS has expanded its role in reviewing J1 waiver applications. HHS’s considerations for a waiver have classically been as follows: (1) the program or activity in which the IMG is engaged is “of high priority and of national or interna-

tional significance in an area of interest” to HHS; (2) the IMG must be an “integral” part of the program or activity “so that the loss of his/her services would necessitate discontinuance of the program or a major phase of it”; and (3) the IMG “must possess outstanding qualifications, training, and experience well beyond the usually expected accomplishments at the graduate, postgraduate, and residency levels and must clearly demonstrate the capability to make original and significant contributions to the program.” Under these criteria, HHS waivers are granted to physicians working in high-level biomedical research.

New rules will also allow HHS to review J1 waiver applications from community health centers, rural hospitals, and other health care providers. In the past, the U.S. Department of Agriculture (USDA) served as the interested federal government agency that reviewed waiver applications to allow foreign doctors to serve in rural underserved communities outside Appalachia, while the Appalachian Regional Commission (ARC) played that role for Appalachian communities. The USDA is no longer handling applications for J1 waivers. HHS will now review waiver applications for primary care practitioners and psychiatrists who have completed residency training within one year of application to practice in designated Health Professional Shortage Areas (HPSAs), Medically Underserved Areas and Populations (MUA/Ps), and Mental Health Professional Shortage Areas (MHPSAs). HHS waiver applications should be mailed to Joyce E. Jones, Executive Secretary, Exchange Visitor Waiver Review Board, Room 639-H, Hubert H. Humphrey Building, Department of Health and Human Services, 200 Independence Avenue, S.W., Washington, D.C. 20201; phone (202) 690-6174; fax (202) 690-7127.

- **The Department of Veterans Affairs.** With more than 170 health care facilities located in various parts of the United States, the VA is a major employer of physicians in this country. In addition, many VA hospitals are affiliated with university medical centers. The VA sponsors IMGs working in research, patient care (regardless of specialty), and teaching. The waiver applicant may engage in teaching and research in conjunction with clinical duties. The VA’s latest guidelines (issued on June 22, 1994) provide that it will act as an interested government agency only when the loss of an IMG’s services would necessitate the discontinuance of a program or a major phase of it and when recruitment efforts have failed to locate a U.S. physician to fill the position.

The procedure for obtaining a VA sponsorship for a J1 waiver is as follows: (1) the IMG should deal directly with the Human Resources Department at the local VA facility; and (2) the facility must request that the VA’s chief medical director sponsor the IMG for a waiver. The waiver request should include the following documentation: (1) a letter from the director of the local facility describing the program, the IMG’s immigration status, the health care needs of the facility, and the facility’s recruitment efforts; (2) recruitment efforts, including copies of all job advertisements run within the preceding year; and (3) copies of the IMG’s licenses, test results, board



certifications, IAP-66 or SEVIS DS-2019 forms, and the like. The VA contact person in Washington, D.C., should be contacted by the local medical facility rather than by IMGs or their attorneys.

- **The Appalachian Regional Commission.** ARC sponsors physicians in certain places in the eastern and southern United States—namely, in Alabama, Georgia, Kentucky, Maryland, Mississippi, New York, North Carolina, Ohio, Pennsylvania, South Carolina, Tennessee, Virginia, and West Virginia. Since 1992, ARC has sponsored approximately 200 primary care IMGs annually in counties within its jurisdiction that have been designated as HPSAs by HHS.

In accordance with its February 1994 revision of its J1 waiver policies, ARC requires that waiver requests initially be submitted to the ARC contact person in the state of intended employment. Contact information for each state can be found on the ARC Web site ([www.arc.gov](http://www.arc.gov)). If the state concurs, a letter from the state's governor recommending the waiver must be addressed to Anne B. Pope, the new federal cochair of ARC. The waiver request should include the following: (1) a letter from the facility to Ms. Pope stating the proposed dates of employment, the IMG's medical specialty, the address of the practice location, an assertion that the IMG will practice primary care for at least 40 hours per week in the HPSA, and details as to why the facility needs the services of the IMG; (2) a J1 Visa Data Sheet; (3) the ARC federal cochair's J1 Visa Waiver Policy and the J1 Visa Waiver Policy Affidavit and Agreement with the notarized signature of the IMG; (4) a contract of at least three years' duration; (5) evidence of the IMG's qualifications, including a résumé, medical diplomas and licenses, and IAP-66 or SEVIS DS-2019 forms; and (6) evidence of unsuccessful attempts to recruit qualified U.S. physicians within the preceding six months. Copies of advertisements, copies of résumés received, and reasons for rejection must also be included. ARC will not sponsor IMGs who have been out of status for six months or longer.

Requests for ARC waivers are then processed in Washington, D.C. (ARC, 1666 Connecticut Avenue, N.W., Washington, D.C. 20009). ARC is usually able to forward a letter confirming that a waiver has been recommended to the requesting facility or attorney within 30 days of the request.

- **The Department of Agriculture.** At the time of publication, the USDA is no longer sponsoring J1 waivers. The scope of the HHS J1 waiver program has been expanded to fill the gap.
- **State Departments of Public Health.** There is no application form for a state-sponsored J1 waiver. However, regulations specify that an application must include the following documents: (1) a letter from the state Department of Public Health identifying the physician and specifying that it would be in the public interest to grant him or her a J1 waiver; (2) an employment contract that is valid for a minimum of three years and that states the name and address of the facility that will employ the physician and the

geographic areas in which he or she will practice medicine; (3) evidence that these geographic areas are located within HPSAs; (4) a statement by the physician agreeing to the contractual requirements; (5) copies of all IAP-66 or SEVIS DS-2019 forms; and (6) a completed U.S. Information Agency (USIA) Data Sheet. Applications are numbered in the order in which they are received, since only 30 physicians per year may be granted waivers in a particular state under the Conrad State 30 program. Individual states may elect to participate or not to participate in this program. At the time of publication, nonparticipating states included Idaho, Oklahoma, and Wyoming, while Texas had suspended its J1 waiver program pending new legislation.

### **The H1B Visa**

Since 1991, the law has allowed medical residency programs to sponsor foreign-born medical residents for H1B visas. There are no restrictions on changing the H1B visa to any other kind of visa, including permanent resident status (green card), through employer sponsorship or through close relatives who are U.S. citizens or permanent residents. It is advisable for SRPs to apply for H1B visas as soon as possible in the official year (beginning October 1) when the new quota officially opens up.

According to the Web site [www.immihelp.com](http://www.immihelp.com), as of October 17, 2000, the following beneficiaries of approved H1B petitions are exempt from the H1B annual cap:

- Beneficiaries who are in J1 nonimmigrant status in order to receive graduate medical education or training, and who have obtained a waiver of the two-year home residency requirement;
- Beneficiaries who are employed at, or who have received an offer of employment at, an institution of higher education or a related or affiliated nonprofit entity;
- Beneficiaries who are employed by, or who have received an offer of employment from, a nonprofit research organization;
- Beneficiaries who are employed by, or who have received an offer of employment from, a governmental research organization;
- Beneficiaries who are currently maintaining, or who have held within the last six years, H1B status, and are ineligible for another full six-year stay as an H1B; and
- Beneficiaries who have been counted once toward the numerical limit and are the beneficiary of multiple petitions.

H1B visas are intended for “professionals” in a “specialty occupation.” This means that an IMG intending to pursue a residency program in the United States with an H1B visa needs to clear all three USMLE Steps before becoming eligible for the H1B. The ECFMG administers Steps 1 and 2, whereas Step 3 is conducted by the individual states. You will need to contact the FSMB or the medical board of the state where you intend to take Step 3 for details (see p. 34, USMLE Step 3 and the IMG).

**H1B Application.** An application for an H1B visa is filed not by the IMG but rather by his or her employment sponsor—in your case, by the SRP in the United States. If an SRP is willing to do so, you will be told about it at the time of your interview for the residency program.

Before filing an H1B application with the DHS, an SRP must file an application with the U.S. Department of Labor affirming that the SRP will pay at least the normal salary for your job that a U.S. professional would earn. After receiving approval from the Labor Department, your SRP should be ready to file the H1B application with the DHS. The SRP's supporting letter is the most important part of the H1B application package; it must describe the job duties to make it clear that the physician is needed in a "specialty occupation" (resident) under the prevalent legal definition of that term.

Most SRPs prefer to issue a SEVIS Form DS-2019 for a J1 visa rather than file papers for an H1B visa because of the burden of paperwork and the attorney costs involved in securing approval of an H1B visa application. Even so, a sizable number of SRPs are willing to go through the trouble, particularly if an IMG is an excellent candidate or if the SRP concerned finds it difficult to fill all the available residency slots (although this is becoming rarer with continuing cuts in residency slots). If an SRP is unwilling to file for an H1B visa because of attorney costs, you could suggest that you would be willing to bear the burden of such costs. The entire process of getting an H1B visa can take anywhere from 10 to 20 weeks.

**H1B Premium Processing Service.** According to the Web site [www.myvisa.com](http://www.myvisa.com), the DHS offers the opportunity to obtain processing of an H1B visa application within 15 calendar days. Within 15 days of receiving Form I-907, the DHS will mail you a notice of approval, request for evidence, intent to deny, or notice of investigation for fraud or misrepresentation. If the notice requires the submission of additional evidence or indicates an intent to deny, a new 15-day period will begin upon delivery to the DHS of a complete response to the request for evidence or notice of intent to deny. The fee for this service is \$1000. With this service, the total time needed to obtain an H1B visa has become significantly shorter than that required for the J1.

Although an H1B visa can be stamped by any U.S. consulate abroad, it is advisable that you have it stamped at the U.S. consulate where you first applied for a visitor visa to travel to the United States for interviews.

### **A Final Word**

IMGs should also be aware of a new program called the National Security Entry-Exit Registration System, which aims to tighten up homeland security by keeping closer tabs on nonimmigrants residing in or entering the United States on temporary visas.

Male citizens or nationals of specific countries who are already residing in the United States may be required to report to a designated DHS office for registration, which includes being fingerprinted, photographed, and interviewed under oath. The official list of countries includes Bangladesh, Egypt, Indonesia, Jordan, Kuwait, Pakistan, Saudi Arabia, Afghanistan, Algeria, Bahrain, Eritrea, Lebanon, Morocco, North Korea, Oman, Qatar, Somalia, Tunisia, the United Arab Emirates, Yemen, Iran, Iraq, Libya, Sudan, and Syria. Different registration deadlines and criteria have been assigned to citizens of the above-mentioned countries, so please refer to <http://uscis.gov> for details.

If you are entering the United States, you may be registered at the port of entry if you are (1) a citizen or national of Iran, Iraq, Libya, Sudan, or Syria; (2) a nonimmigrant who has been designated by the State Department; or (3) any other nonimmigrant identified by immigration officers at airports, seaports, and land ports of entry in accordance with new regulation 8 CFR 264.1(f)(2). If you will be staying in the United States for more than 30 days, you will then be required to register in person at a DHS district office within 30 days for an interview and will be required to reregister annually.

Once you are registered, certain special procedures will apply. If you leave the United States for any reason, you must appear in person before a DHS inspecting officer at a preapproved airport, seaport, or land port and leave the United States from that port on the same day. If you change your address, employment, or school, you must report to the DHS in writing within 10 days using Form AR-11 SR. If any of these regulations are not followed, you may be considered out of status and subject to arrest, detention, fines, and/or removal from the United States, and any further application for immigration may be affected.

For the most up-to-date information regarding policies and procedures, please consult <http://uscis.gov>.

### **Summary**

Despite some significant obstacles, a number of viable methods are available to IMGs who seek visas to pursue a residency program or eventually practice medicine in the United States. There is no doubt that the best alternative for an IMG is to obtain an H1B visa to pursue a medical residency. However, in cases where an IMG joins a residency program with a J1 visa, there are some possibilities for obtaining waivers of the two-year foreign residency requirement, particularly for those who are willing to make a commitment to perform primary care medicine in medically underserved areas.

## Resources for the IMG

### ■ ECFMG

3624 Market Street, Fourth Floor  
Philadelphia, PA 19104-2685  
(215) 386-5900  
Fax: (215) 386-9196  
[www.ecfmg.org](http://www.ecfmg.org)

The ECFMG telephone number is answered only between 9:00 A.M. and 12:30 P.M. and between 1:30 P.M. and 5:00 P.M. Monday through Friday EST. The ECFMG often takes a long time to answer the phone, which is frequently busy at peak times of the year, and then gives you a long voice-mail message—so it is better to write or fax early than to rely on a last-minute phone call. Do not contact the NBME, as all IMG exam matters are conducted by the ECFMG. The ECFMG also publishes an information booklet on ECFMG certification and the USMLE program, which gives details on the dates and locations of forthcoming USMLE and English tests for IMGs together with application forms. It is free of charge and is also available from the public affairs offices of U.S. embassies and consulates worldwide as well as from Overseas Educational Advisory Centers. You may order single copies of the handbook by calling (215) 386-5900, preferably on weekends or between 6 P.M. and 6 A.M. Philadelphia time, or by faxing to (215) 387-9963. Requests for multiple copies must be made by fax or mail on organizational letterhead. The full text of the booklet is also available on the ECFMG's Web site at [www.ecfmg.org](http://www.ecfmg.org).

### ■ FSMB

P.O. Box 619850  
Dallas, TX 75261-9850  
(817) 868-4000  
Fax: (817) 868-4099  
[www.fsmb.org](http://www.fsmb.org)

The FSMB has a number of publications available, including *The Exchange, Section I*, which gives detailed information on examination and licensing requirements in all U.S. jurisdictions. The cost is \$30. (Texas residents must add 8.25% state sales tax.) To obtain these publications, submit the online order form. Payment options include Visa or MasterCard. Alternatively, write to Federation Publications at the above address. All orders must be prepaid with a personal check drawn on a U.S. bank, a cashier's check, or a money order payable to the federation. Foreign orders must be accompanied by an international money order or the equivalent, payable in U.S. dollars through a U.S. bank or a U.S. affiliate of a foreign bank. For Step 3 inquiries, the telephone number is (817) 868-4041. You may e-mail the FSMB at [usmle@fsmb.org](mailto:usmle@fsmb.org) or write to Examination Services at the address above.

- Immigration information for IMGs is available from the sites of Siskind Susser, a firm of attorneys specializing in immigration law: [www.visalaw.com/IMG/resources.html](http://www.visalaw.com/IMG/resources.html).
- Another source of immigration information can be found on the Web site of the law offices of Carl Shusterman, a Los Angeles attorney specializing in medical immigration law: [www.shusterman.com](http://www.shusterman.com).
- The AMA has dedicated a portion of its Web site to information on IMG demographics, residencies, immigration, and the like: [www.ama-assn.org/ama/pub/category/17.html](http://www.ama-assn.org/ama/pub/category/17.html).
- International Medical Placement Ltd., a U.S. company specializing in recruiting foreign physicians to work in the United States, has a site at [www.intlmedicalplacement.com](http://www.intlmedicalplacement.com).
- Two more useful Web sites are [www.myvisa.com](http://www.myvisa.com) and [www.immihelp.com](http://www.immihelp.com).
- *First Aid for the International Medical Graduate*, 2nd ed., by Keshav Chander (2002; 313 pages; ISBN 0071385320), is an excellent resource written by a successful IMG. The book includes interviews with successful IMGs and students gearing up for the USMLE, complete “getting settled” information for new residents, and tips for dealing with possible social and cultural transition difficulties. The book provides useful advice on the U.S. curriculum, the health care delivery system, and ethical issues—and the differences IMGs should expect. Dr. Chander points out the weaknesses often found in IMG hopefuls and suggests ways to improve their performance on standardized tests as well as on academic and clinical evaluations. As a bonus, the guide contains information on how to get good fellowships after residency. The bottom line is that this is a reassuring guide that can help IMGs boost their confidence and proficiency. A great “first of its kind” that will empower IMGs with information that they need to succeed.

Other books that may be useful and of interest to IMGs are as follows:

- *International Medical Graduates in U.S. Hospitals: A Guide for Directors and Applicants*, by Faroque A. Khan and Lawrence G. Smith (1995; ISBN 094312641x).
- *Insider's Guide for the International Medical Graduate to Obtain a Medical Residency in the U.S.A.*, by Ahmad Hakemi (1999; ISBN 1929803001).

## ► FIRST AID FOR THE OSTEOPATHIC MEDICAL STUDENT

**What Is the COMLEX Level 1?**

In 1995, the National Board of Osteopathic Medical Examiners (NBOME) introduced a new assessment tool called the Comprehensive Osteopathic Medical Licensing Examination, or COMLEX-USA. As with the former NBOME examination series, the COMLEX-USA is administered over three levels. In 1995, only Level 3 was administered, but by 1998 all three levels were implemented. The COMLEX-USA is now the only exam offered to osteopathic students. One goal of this changeover is to have all 50 states recognize this examination as equivalent to the USMLE. Currently, the COMLEX-USA exam sequence is accepted for licensure in all 50 states.

The COMLEX-USA series assesses osteopathic medical knowledge and clinical skills using clinical presentations and physician tasks. A description of the COMLEX-USA Written Examination Blueprints for each level, which outline the various clinical presentations and physician tasks that examinees will encounter, is given on the NBOME Web site. Another stated goal of the COMLEX-USA Level 1 is to create a more primary care-oriented exam that integrates osteopathic principles into clinical situations. As of July 1, 2004, the NBOME has initiated the administration of a Performance Evaluation/Clinical Skills component of the COMLEX-USA designated Level 2-PE, which candidates must pass in order to be eligible for the COMLEX Level 3.

To be eligible to take the COMLEX-USA Level 1, you must have satisfactorily completed at least one-half of your sophomore year in an American Osteopathic Association (AOA)-approved medical school. In addition, you must obtain verification that you are in good standing at your medical school via approval of your dean. Applications may be downloaded from the NBOME Web site.

For all three levels of the COMLEX-USA, raw scores are converted to a percentile score and a score ranging from 5 to 800. For Levels 1 and 2, a score of 400 is required to pass; for Level 3, a score of 350 is needed. COMLEX-USA scores are usually mailed eight weeks after the test date. The mean score is always 500. From 2002 through October 2005, the standard deviation for Level 1 was 79.

If you pass a COMLEX-USA examination, you are not allowed to retake it to improve your grade. If you fail, there is no specific limit to the number of times you can retake it in order to pass. Level 2 and 3 exams must be passed in sequential order within seven years of passing Level 1.

**What Is the Structure of the COMLEX Level 1?**

The final paper-and-pencil COMLEX Level 1 examination was administered on October 11–12, 2005. Last year, the NBOME began delivering the COMLEX Level 1 by computer. This conversion to a computer-based examination

reduced the test duration from two days to one day, decreased the total number of questions from about 800 to 400, and decreased the total testing time from 16 hours to 8 hours.

The computer-based COMLEX Level 1 examination consists of multiple-choice questions in the same format as that of the old paper-and-pencil COMLEX Level 1 examination. Most of the questions are in one-best-answer format, but a small number are matching-type questions. Some one-best-answer questions are bundled together around a common question stem that usually takes the form of a clinical scenario. New question formats may gradually be introduced, but candidates will be notified if this occurs.

Questions are grouped into sections of 50 questions, each in a manner similar to the USMLE. Reviewing and changing answers may be done only in the current section. A “review page” will be presented for each block in order to advise test takers of questions completed, questions marked for further review, and incomplete questions for which no answer has been given.

Only three optional breaks are permitted during the test session. These breaks are offered after the first two sections of the morning or afternoon session have been completed. The first optional 10-minute break is offered in the morning session after completion of section 2. The second optional 10-minute break is offered in the afternoon session after completion of section 6. These two blocks count against the total exam time. A 40-minute lunch break is also optional, but it will not count against the total exam time. This break may be taken after completion of section 4. This is an important departure from the USMLE. More information about the computer-based COMLEX-USA examinations can be obtained from [www.nbome.org](http://www.nbome.org).

### **What Is the Difference Between the USMLE and the COMLEX-USA?**

Although the COMLEX-USA and the USMLE are similar in scope, content, and emphasis, some differences are worth noting. For example, the COMLEX-USA Level 1 tests osteopathic principles in addition to basic science materials but does not emphasize lab techniques. In addition, although both exams often require that you apply and integrate knowledge over several areas of basic science to answer a given question, many students who took both tests in 2004 reported that the questions differed somewhat in style. Students reported, for example, that USMLE questions generally required that the test taker reason and draw from the information given (often a two-step process), whereas those on the COMLEX-USA exam tended to be more straightforward. Furthermore, USMLE questions were on average found to be considerably longer than those on the COMLEX-USA.

Students also commented that the COMLEX-USA utilized “buzzwords,” although limited in their use (e.g., “rose spots” in typhoid fever), whereas the USMLE avoided buzzwords in favor of descriptions of clinical findings or symptoms (e.g., rose-colored papules on the abdomen rather than rose spots).



Finally, the 2004 USMLE had many more photographs than did the COMLEX-USA. In general, the overall impression was that the USMLE was a more “thought-provoking” exam, while the COMLEX-USA was more of a “knowledge-based” exam.

### Who Should Take Both the USMLE and the COMLEX-USA?

Aside from facing the COMLEX-USA Level 1, you must decide if you will also take the USMLE Step 1. We recommend that you consider taking both the USMLE and the COMLEX-USA under the following circumstances:

- **If you are applying to allopathic residencies.** Although there is growing acceptance of COMLEX-USA certification on the part of allopathic residencies, some allopathic programs prefer or even require passage of the USMLE Step 1. These include many academic programs, programs in competitive specialties (e.g., orthopedics, ophthalmology, or dermatology), and programs in competitive geographic areas (such as California). Fourth-year doctor of osteopathy (DO) students who have already matched may be a good source of information about which programs and specialties look for USMLE scores. It is also a good idea to contact program directors at the institutions you are interested in to ask about their policy regarding the COMLEX-USA versus the USMLE.
- **If you are unsure about your postgraduate training plans.** Successful passage of both the COMLEX-USA Level 1 and the USMLE Step 1 is certain to provide you with the greatest possible range of options when you are applying for internship and residency training.

The clinical coursework that some DO students receive during the summer of their third year (as opposed to their starting clerkships) is considered helpful in integrating basic science knowledge for the COMLEX-USA or the USMLE.

### How Do I Prepare for the COMLEX-USA Level 1?

Student experience suggests that you should start studying for the COMLEX-USA four to six months before the test is given, as an early start will allow you to spend up to a month on each subject. The recommendations made in Section I regarding study and testing methods, strategies, and resources, as well as the books suggested in Section IV for the USMLE Step 1, hold true for the COMLEX-USA as well.

Another important source of information is in the *Examination Guidelines and Sample Exam*, a booklet that discusses the breakdown of each subject while also providing sample questions and corresponding answers. Many students, however, felt that this breakdown provided only a general guideline and was not representative of the level of difficulty of the actual COMLEX-USA. The sample questions did not provide examples of clinical vignettes, which made up approximately 25% of the exam. You will receive this publication with registration materials for the COMLEX-USA Level 1 exam, but you can also receive a copy and additional information by writing:

**NBOME**

8765 W. Higgins Road, Suite 200  
 Chicago, IL 60631-4174  
 (773) 714-0622  
 Fax: (773) 714-0631

or by visiting the NBOME Web page at [www.nbome.org](http://www.nbome.org).

*Level 1 Practice Items* is a new feature offered by the NBOME. It contains about 200 COMLEX-USA Level 1 items and answers. It is important to note that items in this booklet have been used in previous exams. The booklet costs \$8 and can be purchased via the NBOME Web site.

The 2006 COMLEX-USA exam consisted of 120 multiple-choice questions and 80 clinical vignette questions per test booklet. There were four test booklets, two of which had approximately ten matching questions. Each multiple-choice question accompanied a small case (about one to two sentences long).

In 2006, students reported an emphasis in certain areas. For example:

- There was an increased emphasis on upper limb anatomy/brachial plexus.
- Specific topics were repeatedly tested on the exam. These included cardiovascular physiology and pathology, acid-base physiology, diabetes, benign prostatic hyperplasia, sexually transmitted diseases, measles, and rubella. Thyroid and adrenal function, neurology (head injury), specific drug treatments for bacterial infection, migraines/cluster headaches, and drug mechanisms also received heavy emphasis.
- Behavioral science questions were based on psychiatry.
- High-yield osteopathic manipulative technique (OMT) topics on the 2006 exam included an extremely heavy emphasis on the sympathetic and parasympathetic innervations of viscera and nerve roots, rib mechanics/diagnosis, and basic craniosacral theory.

Since topics that were repeatedly tested appeared in all four booklets, students found it useful to review them in between the two test days. It is important to understand that the topics emphasized on the 2006 exam may not be stressed on the 2007 exam. However, some topics are heavily tested each year, so it may be beneficial to have a solid foundation of the above-mentioned topics.

## ► FIRST AID FOR THE PODIATRIC MEDICAL STUDENT

The National Board of Podiatric Medical Examiners (NBPME) tests are designed to assess whether a candidate possesses the knowledge required to practice as a minimally competent entry-level podiatrist. The NBPME examinations are used as part of the licensing process governing the practice of podiatric medicine. The NBPME exam is recognized by all 50 states and the District of Columbia, the U.S. Army, the U.S. Navy, and the Canadian provinces of Alberta, British Columbia, and Ontario. Individual states use the examination scores differently; therefore, doctor of podiatric medicine (DPM) candidates should refer to the *NBPME Bulletin of Information: 2007 Examinations*.

The NBPME Part I is generally taken after the completion of the second year of podiatric medical education. Unlike the USMLE Step 1, there is no behavioral science section, nor is biomechanics tested on the NBPME Part I. The exam samples seven basic science disciplines: general anatomy (10%); lower extremity anatomy (22%); biochemistry (10%); physiology (12%); medical microbiology and immunology (15%); pathology (15%); and pharmacology (16%). A detailed outline of topics and subtopics covered on the exam can be found in the *NBPME Bulletin of Information*, available on the NBPME Web site.

### **Your NBPME Appointment**

In early spring, your college registrar will have you fill out an application for the NBPME Part I. After your application and registration fees are received, you will be mailed the *NBPME Bulletin of Information: 2007 Examinations*. The exam will be offered at an independent location in each city with a podiatric medical school (New York, Philadelphia, Miami, Cleveland, Chicago, Des Moines, Phoenix, and San Francisco). You may take the exam at any of these locations regardless of which school you attend. However, you must designate on your application which testing location you desire. Specific instructions about dates the exam is offered and registration deadlines can be found in the *NBPME Bulletin*.

### **Exam Format**

The NBPME Part I is a written exam of 150 questions. The test consists entirely of multiple-choice questions with four answer choices. Examinees have three hours in which to take the exam and are given scratch paper and a calculator, both of which must be turned in at the end of the exam. Some questions on the exam will be “trial questions.” These questions are evaluated as future board questions but are not counted in your score.

### **Interpreting Your Score**

Three to four weeks following the exam date, test takers will receive their scores by mail. NBPME scores are reported as pass/fail, with a scaled score of

at least 75 needed to pass. Eighty-five percent of first-time test takers pass the NBPME Part I. Failing candidates receive a report with one score between 55 and 74 in addition to diagnostic messages intended to help identify strengths or weaknesses in specific content areas. If you fail the NBPME Part I, you must retake the entire examination at a later date. There is no limit to the number of times you can retake the exam.

### **Preparation for the NBPME Part I**

Students suggest that you begin studying for the NBPME Part I at least three months prior to the test date. The suggestions made in Section I regarding study and testing methods for the USMLE Step 1 can be applied to the NBPME as well. This book should, however, be used as a supplement and not as the sole source of information. Keep in mind that you need only a passing score. Neither you nor your school or future residency will ever see your actual numerical score. Competing with colleagues should not be an issue, and study groups are beneficial to many.

A potential study method that helps many students is to copy the outline of the material to be tested from the *NBPME Bulletin*. Check off each topic during your study, thus ensuring you have engaged each topic. If you are pressed for time, prioritize subjects based on their weight on the exam. Approximately 22% of the NBPME Part I focuses on lower extremity anatomy. In this area, students should rely on the notes and material that they received from their class. Remember, lower extremity anatomy is the podiatric physician's specialty—so everything about it is important. Do not forget to study osteology. Keep your old tests and look through old lower extremity class exams, since each of the podiatric colleges submits questions from its own exams. This strategy will give you an understanding of the types of questions that may be asked. On the NBPME Part I, you will see some of the same classic lower extremity anatomy questions you were tested on in school.

The NBPME, like the USMLE, requires that you apply and integrate knowledge over several areas of basic science in order to answer the questions. Students report that many questions emphasize clinical presentations; however, the facts in this book are very useful in helping students recall the various diseases and organisms. DPM candidates should expand on the high-yield pharmacology section and study antifungal drugs and treatments for *Pseudomonas*, methicillin-resistant *S. aureus*, candidiasis, and erythrasma. The high-yield section focusing on pathology is very useful; however, additional emphasis on diabetes mellitus and all its secondary manifestations, particularly peripheral neuropathy, should not be overlooked. Students should also focus on renal physiology and drug elimination, the biochemistry of gout, and neurophysiology, all of which have been noted to be important topics on the NBPME Part I exam.

A sample set of questions is found in the *NBPME Bulletin of Information: 2007 Examinations*. These samples are similar in difficulty to actual board

questions. If you do not receive an *NBPME Bulletin* or if you have any questions regarding registration, fees, test centers, authorization forms, or score reports, please contact your college registrar or:

**NBPME**

P.O. Box 510

Bellefonte, PA 16823

(814) 357-0487

Fax: (814) 357-0581

E-mail: NBPMEOfc@aol.com

or visit the NBPME Web page at [www.nbpme.info](http://www.nbpme.info).

## ► FIRST AID FOR THE STUDENT WITH A DISABILITY

The USMLE provides accommodations for students with documented disabilities. The basis for such accommodations is the Americans with Disabilities Act (ADA) of 1990. The ADA defines a disability as “a significant limitation in one or more major life activities.” This includes both “observable/physical” disabilities (e.g., blindness, hearing loss, narcolepsy) and “hidden/mental disabilities” (e.g., attention-deficit hyperactivity disorder, chronic fatigue syndrome, learning disabilities).

To provide appropriate support, the administrators of the USMLE must be informed of both the nature and the severity of an examinee’s disability. Such documentation is required for an examinee to receive testing accommodations. Accommodations include extra time on tests, low-stimulation environments, extra or extended breaks, and zoom text.

### **Who Can Apply for Accommodations?**

Students or graduates of a school in the United States or Canada that is accredited by the Liaison Committee on Medical Education (LCME) or the AOA may apply for test accommodations directly from the NBME. Requests are granted only if they meet the ADA definition of a disability. If you are a disabled student or a disabled graduate of a foreign medical school, you must contact the ECFMG (see below).

### **Who Is Not Eligible for Accommodations?**

Individuals who do not meet the ADA definition of disabled are not eligible for test accommodations. Difficulties not eligible for test accommodations include test anxiety, slow reading without an identified underlying cognitive deficit, English as a second language, and learning difficulties that have not been diagnosed as a medically recognized disability.

### **Understanding the Need for Documentation**

Although most learning-disabled medical students are all too familiar with the often exhausting process of providing documentation of their disability, you should realize that **applying for USMLE accommodation is different from these previous experiences**. This is because the NBME determines whether an individual is disabled solely on the basis of the guidelines set by the ADA. Previous accommodation does not in itself justify provision of an accommodation, so be sure to review the NBME guidelines carefully.

### **Getting the Information**

The first step in applying for USMLE special accommodations is to contact the NBME and obtain a guidelines and questionnaire booklet. This can be obtained by calling or writing to:

**Testing Coordinator**

Office of Test Accommodations  
National Board of Medical Examiners  
3750 Market Street  
Philadelphia, PA 19104-3102  
(215) 590-9700

Internet access to this information is also available at [www.nbme.org](http://www.nbme.org). This information is also relevant for IMGs, since the information is the same as that sent by the ECFMG.

Foreign graduates should contact the ECFMG to obtain information on special accommodations by calling or writing to:

**ECFMG**

3624 Market Street, Fourth Floor  
Philadelphia, PA 19104-2685  
(215) 386-5900

When you get this information, take some time to read it carefully. The guidelines are clear and explicit about what you need to do to obtain accommodations.

The 2007 edition of *First Aid for the USMLE Step 1* contains a revised and expanded database of basic science material that student authors and faculty have identified as high yield for board reviews. The information is presented in a partially organ-based format. Hence, Section II is devoted to the pathology, foundational principles of behavioral science, biochemistry, embryology, microbiology and immunology, and pharmacology. Section III focuses on organ systems, with subsections covering the embryology, anatomy and histology, physiology, pathology, and pharmacology relevant to each. Each subsection is then divided into smaller topic areas containing related facts. Individual facts are generally presented in a three-column format, with the **Title** of the fact in the first column, the **Description** of the fact in the second column, and the **Mnemonic** or **Special Note** in the third column. Some facts do not have a mnemonic and are presented in a two-column format. Others are presented in list or tabular form in order to emphasize key associations.

The database structure used in Sections II and III is useful for reviewing material already learned. These sections are **not** ideal for learning complex or highly conceptual material for the first time. At the beginning of each subsection, we list supplementary high-yield clinical vignettes and topics that have appeared on recent exams in order to help focus your review.

The database of high-yield facts is not comprehensive. Use it to complement your core study material and not as your primary study source. The facts and notes have been condensed and edited to emphasize the essential material, and as a result each entry is “incomplete.” Work with the material, add your own notes and mnemonics, and recognize that not all memory techniques work for all students.

We update the database of high-yield facts annually to keep current with new trends in boards content as well as to expand our database of information. However, we must note that inevitably many other very high yield entries and topics are not yet included in our database.

We actively encourage medical students and faculty to submit entries and mnemonics so that we may enhance the database for future students. We also solicit recommendations of alternate tools for study that may be useful in preparing for the examination, such as diagrams, charts, and computer-based tutorials (see How to Contribute, p. xv).

### Disclaimer

The entries in this section reflect student opinions of what is high yield. Owing to the diverse sources of material, no attempt has been made to trace or reference the origins of entries individually. We have regarded mnemonics as essentially in the public domain. All errors and omissions will gladly be corrected if brought to the attention of the authors, either through the publisher or directly by e-mail.



# HIGH-YIELD PRINCIPLES IN

## Behavioral Science

*"It's psychosomatic. You need a lobotomy. I'll get a saw."*

—Calvin, "Calvin & Hobbes"

A heterogeneous mix of epidemiology, biostatistics, ethics, psychology, sociology, and more falls under this heading. Many medical students do not study this discipline diligently because the material is felt to be "easy" or "common sense." In our opinion, this is a missed opportunity.

Many students feel that some behavioral science questions are less concrete and require an awareness of the social aspects of medicine. For example: If a patient does or says something, what should you do or say in response? These so-called quote questions now constitute much of the behavioral science section. We have included several examples in the high-yield clinical vignettes. Medical ethics and medical law are also appearing with increasing frequency. In addition, the key aspects of the doctor-patient relationship (e.g., communication skills, open-ended questions, facilitation, silence) are high yield. Basic biostatistics and epidemiology are very learnable and high yield. Be able to apply biostatistical concepts such as specificity and predictive values in a problem-solving format.

- ▶ High-Yield Clinical Vignettes
- ▶ Epidemiology/Biostatistics
- ▶ Ethics
- ▶ Development
- ▶ Physiology
- ▶ Psychology

## BEHAVIORAL SCIENCE—HIGH-YIELD CLINICAL VIGNETTES

■ Woman with anxiety about a gynecologic exam is told to relax and to imagine going through the steps of the exam.	What process does this exemplify?	Systematic desensitization.
■ 65-year-old man is diagnosed with incurable metastatic pancreatic adenocarcinoma. His family asks you, the doctor, not to tell the patient.	What do you do?	Assess whether telling patient will negatively affect his health. If not, tell him.
■ Man admitted for chest pain is medicated for ventricular tachycardia. The next day he jumps out of bed and does 50 pushups to show the nurses he has not had a heart attack.	What defense mechanism is he using?	Denial.
■ You find yourself attracted to your 26-year-old patient.	What do you say?	Nothing! The tone of the interview must be very professional; it is not acceptable to have any sort of romantic relationship with patients. If you feel your actions may be misinterpreted, invite a chaperone into the room.
■ Large group of people is followed over 10 years. Every 2 years, it is determined who develops heart disease and who does not.	What type of study is this?	Cohort study.
■ Girl can groom herself, can hop on one foot, and has an imaginary friend.	How old is she?	Four years old.
■ Man has flashbacks about his girlfriend's death 2 months ago following a hit-and-run accident. He often cries and wishes for the death of the culprit.	What is the diagnosis?	Normal bereavement.
■ 36-year-old woman with a strong family history of breast cancer refuses a mammogram because she heard it hurts.	What do you do?	Discuss the risks and benefits of not having a mammogram. Each patient must give her own informed consent to each procedure; if the patient refuses, you must abide by her wishes.

- |                                                                                                                                                                                                                  |                                      |                                                                                                                                                                                                                                                                            |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>■ 4-year-old girl complains of a burning feeling in her genitalia; otherwise, she behaves and sleeps normally. Smear of discharge shows <i>N. gonorrhoeae</i>.</li> </ul> | <p>How was she infected?</p>         | <p>Sexual abuse.</p>                                                                                                                                                                                                                                                       |
| <ul style="list-style-type: none"> <li>■ 72-year-old man insists on stopping treatment for his heart condition because it makes him feel “funny.”</li> </ul>                                                     | <p>What do you do?</p>               | <p>Although you want to encourage the patient to take his medication, the patient has the final say in his own treatment regimen. You should investigate the “funny” feeling and determine if there are drugs available that don’t elicit this particular side effect.</p> |
| <ul style="list-style-type: none"> <li>■ During a particular stage of sleep, man has variable blood pressure, penile tumescence, and variable EEG.</li> </ul>                                                    | <p>What stage of sleep is he in?</p> | <p>REM sleep.</p>                                                                                                                                                                                                                                                          |

## ► BEHAVIORAL SCIENCE—EPIDEMIOLOGY/BIOSTATISTICS

**Types of Studies**

Study type	Design	Measure/example
<b>Case-control study</b> Observational Retrospective	Compare a group of people with disease to a group without.	<b>Odds ratio (OR).</b> “Patients with COPD had higher odds of a history of smoking than those without COPD.”
<b>Cohort study</b> Observational Prospective	Compare a group with a given risk factor to a group without, to assess whether the risk factor increases the likelihood of disease.	<b>Relative risk (RR).</b> “Smokers had a higher risk of developing COPD than did nonsmokers.”
<b>Cross-sectional study</b> Observational	Collect data from a group of people to assess frequency of disease (and related risk factors) at a particular point in time.	Measures disease prevalence. Can show risk factor association with disease, but not causality.
<b>Twin concordance study</b>	Compare the frequency with which both monozygotic twins or both dizygotic twins develop a disease.	Measures heritability.
<b>Adoption study</b>	Compare siblings raised by biologic vs. adoptive parents.	Measures heritability and influence of environmental factors.

**Clinical Trials**

	Experimental study. Compares therapeutic benefits of two or more treatments, or treatment and placebo.	Highest-quality study when randomized and double-blinded.
<b>Phase I</b>	<b>Study sample</b> Small number of patients, usually normal volunteers.	<b>Purpose</b> Assess safety, toxicity, and pharmacokinetics.
<b>Phase II</b>	Small number of patients with disease of interest.	Assess treatment efficacy, optimal dosing, and adverse effects.
<b>Phase III</b>	Large number of patients randomly assigned to either the treatment under investigation or to the best available treatment (or placebo).	Compare the new treatment to the current standard of care. Is more convincing if double-blind (i.e., neither patient nor doctor knows which drug the patient is taking).

**Meta-analysis**

	Pools data from several studies. Achieves greater statistical power and integrates results of similar studies. Highest echelon of clinical evidence.	May be limited by quality of individual studies or bias in study selection.
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**Prevalence vs. incidence**

$$\text{Prevalence} = \frac{\text{total cases in population at a given time}}{\text{total population at risk}}$$

$$\text{Incidence} = \frac{\text{new cases in population over a given time period}}{\text{total population at risk during that time}}$$

Prevalence  $\cong$  incidence  $\times$  disease duration.

Prevalence  $>$  incidence for chronic diseases (e.g., diabetes).

Prevalence = incidence for acute disease (e.g., common cold).

**Incidence** is new **incidents**.

When calculating incidence, don't forget that people previously positive for a disease are no longer considered at risk.

**Evaluation of Diagnostic Tests**

Uses 2 x 2 table comparing test results with the actual presence of disease.

		Disease	
		$\oplus$	$\ominus$
Test	$\oplus$	a	b
	$\ominus$	c	d

**Sensitivity**

Percent of people with disease who test positive.  
High value is desirable for ruling **out** disease (low false-negative rate).

$$= a / (a + c)$$

$$= 1 - \text{percent false-negatives}$$

**SNOUT** = SeNsitivity rules **OUT**.

**Specificity**

Percent of people without disease who test negative.  
High value is desirable for ruling **in** disease (low false-positive rate).

$$= d / (d + b)$$

$$= 1 - \text{percent false-positives}$$

**SPIN** = SPecificity rules **IN**.

**Positive predictive value (PPV)**

Percent of positive test results that are true-positive.  
Probability that person actually has the disease given a positive test result.

$$= a / (a + b)$$

**Negative predictive value (NPV)**

Percent of negative test results that are true-negative.  
Probability that person actually is disease free given a negative test result.

$$= d / (c + d)$$

**Odds ratio vs. relative risk****Odds ratio (OR)**  
for case control studies

Odds of having disease in exposed group divided by odds of having disease in unexposed group.  
Approximates relative risk if prevalence of disease is not too high.

**Relative risk (RR)**  
for cohort studies

Relative probability of getting a disease in the exposed group compared to the unexposed group  
Calculated as percent with disease in exposed group divided by percent with disease in unexposed group

**Attributable risk**

The difference in risk between exposed and unexposed groups, i.e., also the percent of disease occurrences that are a result of the exposure (e.g., smoking causes one-third of cases of pneumonia).

		Disease	
		$\oplus$	$\ominus$
Risk Factor	$\oplus$	a	b
	$\ominus$	c	d

$$\text{Odds ratio} = \frac{a/b}{c/d} = \frac{ad}{bc}$$

$$\text{Relative risk} = \frac{a/(a + b)}{c/(c + d)}$$

$$\text{Attributable risk} = \frac{a}{a + b} - \frac{c}{c + d}$$

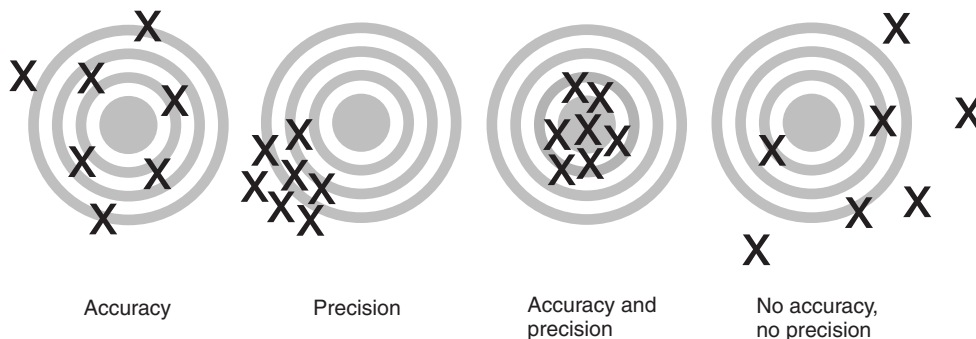
► BEHAVIORAL SCIENCE—EPIDEMIOLOGY/BIOSTATISTICS (*continued*)**Precision vs. accuracy**

Precision is:

1. The consistency and reproducibility of a test (reliability)
2. The absence of random variation in a test

Accuracy is the trueness of test measurements (validity).

Random error—reduced precision in a test.  
Systematic error—reduced accuracy in a test.

**Bias**

Occurs when one outcome is systematically favored over another.

1. **Selection bias**—nonrandom assignment to study group
2. **Recall bias**—knowledge of presence of disorder alters recall by subjects
3. **Sampling bias**—subjects are not representative; therefore, results are not generalizable
4. **Late-look bias**—information gathered at an inappropriate time

Ways to reduce bias:

1. Blind studies (double blind is better)
2. Placebo responses
3. Crossover studies (each subject acts as own control)
4. Randomization

**Statistical distribution**

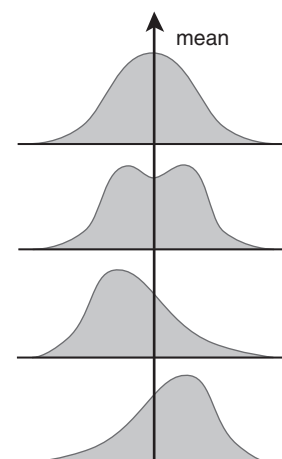
Terms that describe statistical distributions:

Normal  $\approx$  Gaussian  $\approx$  bell-shaped (mean = median = mode).

Bimodal is simply 2 humps.

Positive skew is asymmetry with tail on the right (mean > median > mode).

Negative skew has tail on the left (mean < median < mode).



**Statistical hypotheses**

Null ( $H_0$ )	Hypothesis of no difference (e.g., there is no association between the disease and the risk factor in the population).
Alternative ( $H_1$ )	Hypothesis that there is some difference (e.g., there is some association between the disease and the risk factor in the population).

		Reality	
		$H_1$	$H_0$
Study results	$H_1$	Power ( $1 - \beta$ )	$\alpha$
	$H_0$	$\beta$	

**Type I error ( $\alpha$ )**

Stating that there **is** an effect or difference when none exists (to mistakenly accept the experimental hypothesis and reject the null hypothesis).  $p$  is judged against  $\alpha$ , a preset level of significance (usually  $< .05$ ).  
 $p$  = probability of making a type I error.

If  $p < .05$ , then there is less than a 5% chance that the data will show something that is not really there.  $\alpha$  = you “saw” a difference that did not exist—for example, convicting an innocent man.

**Type II error ( $\beta$ )**

Stating that there **is not** an effect or difference when one exists (to fail to reject the null hypothesis when in fact  $H_0$  is false).  $\beta$  is the probability of making a type II error.

$\beta$  = you did not “see” a difference that does exist—for example, setting a guilty man free.

**Power ( $1 - \beta$ )**

Probability of rejecting null hypothesis when it is in fact false, or the likelihood of finding a difference if one in fact exists. It depends on:

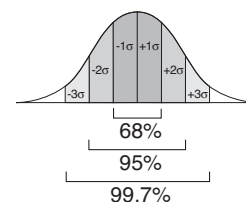
1. Total number of end points experienced by population
2. Difference in compliance between treatment groups (differences in the mean values between groups)
3. Size of expected effect

If you  $\uparrow$  sample size, you  $\uparrow$  power. There is power in numbers.  
 Power =  $1 - \beta$ .

**Standard deviation vs. standard error**

$n$  = sample size.  
 $\sigma$  = standard deviation.  
 SEM = standard error of the mean.  
 $SEM = \sigma / \sqrt{n}$ .  
 Therefore,  $SEM < \sigma$  and SEM decreases as  $n$  increases.

Normal (Gaussian) distribution:

**Confidence interval**

Range of values in which a specified probability of the means of repeated samples would be expected to fall.  
 CI = confidence interval.  
 CI = range from  $[\text{mean} - Z(SEM)]$  to  $[\text{mean} + Z(SEM)]$ .  
 The 95% CI (corresponding to  $p = .05$ ) is often used. For the 95% CI,  $Z = 1.96$ .

If the 95% CI for a mean difference between 2 variables includes 0, then there is no significant difference and  $H_0$  is not rejected. If the 95% CI for odds ratio or relative risk includes 1,  $H_0$  is not rejected.

► BEHAVIORAL SCIENCE–EPIDEMIOLOGY/BIOSTATISTICS (*continued*)

<b>t-test vs. ANOVA vs. <math>\chi^2</math></b>	<p>t-test checks difference between the means of 2 groups.</p> <p>ANOVA checks difference between the means of 3 or more groups.</p> <p><math>\chi^2</math> checks difference between 2 or more percentages or proportions of categorical outcomes (not mean values).</p>	<p>Mr. T is mean.</p> <p>ANOVA = ANalysis Of VAriance of 3 or more variables.</p> <p><math>\chi^2</math> = compare percentages (%) or proportions.</p>
<b>Correlation coefficient (r)</b>	<p>r is always between -1 and +1. Absolute value indicates strength of correlation between 2 variables.</p> <p>Coefficient of determination = <math>r^2</math>.</p>	
<b>Disease prevention</b>	<p>1°—prevent disease occurrence (e.g., vaccination).</p> <p>2°—early detection of disease (e.g., Pap smear).</p> <p>3°—reduce disability from disease (e.g., exogenous insulin for diabetes).</p>	<p><b>PDR:</b></p> <p>Prevent</p> <p>Detect</p> <p>Reduce disability</p>
<b>Important prevention measures</b>		
<b>Risk factor</b>	<b>Services</b>	
Diabetes	Eye, foot exams; urine tests	
Drug use	Hepatitis immunizations; HIV, TB tests	
Alcoholism	Influenza, pneumococcal immunizations; TB test	
Overweight	Blood sugar tests for diabetes	
Homeless, recent immigrant, inmate	TB test	
High-risk sexual behavior	HIV, hepatitis B, syphilis, gonorrhea, chlamydia tests	
<b>Reportable diseases</b>	<p>Only some infectious diseases are reportable in all states, including AIDS, chickenpox, gonorrhea, hepatitis A and B, measles, mumps, rubella, salmonella, shigella, syphilis, and TB.</p> <p>Other diseases (including HIV) vary by state.</p>	<p><b>B. A. SSSMMART</b></p> <p><b>Chicken</b> or you're <b>Gone</b>:</p> <p>Hep B</p> <p>Hep A</p> <p>Salmonella</p> <p>Shigella</p> <p>Syphilis</p> <p>Measles</p> <p>Mumps</p> <p>AIDS</p> <p>Rubella</p> <p>Tuberculosis</p> <p>Chickenpox</p> <p>Gonorrhea</p>



**Leading causes of death in the United States by age**

Infants	Congenital anomalies, short gestation/low birth weight, sudden infant death syndrome, maternal complications of pregnancy, respiratory distress syndrome.
Age 1–14	Injuries, cancer, congenital anomalies, homicide, heart disease.
Age 15–24	Injuries, homicide, suicide, cancer, heart disease.
Age 25–64	Cancer, heart disease, injuries, suicide, stroke.
Age 65+	Heart disease, cancer, stroke, COPD, pneumonia, influenza.

**Medicare and Medicaid**

Medicare and Medicaid are federal programs that originated from amendments to the Social Security Act.  
 Medicare Part A = hospital; Part B = doctor bills.  
 Medicaid is federal and state assistance for very low income people.

Medicar**E** is for **E**lderly.  
 Medicaid**I** is for **D**estitute.

**► BEHAVIORAL SCIENCE—ETHICS****Core ethical principles**

Autonomy	Obligation to respect patients as individuals and to honor their preferences in medical care.
Beneficence	Physicians have a special ethical (fiduciary) duty to act in the patient's best interest. May conflict with autonomy. If the patient can make an informed decision, ultimately, the patient has the right to decide.
Nonmaleficence	"Do no harm." However, if benefits of an intervention outweigh the risks, a patient may make an informed decision to proceed (most surgeries fall into this category).
Justice	To treat persons fairly.

**Informed consent**

Legally requires:

1. Discussion of pertinent information
2. Patient's agreement to the plan of care
3. Freedom from coercion

Patients must understand the risks, benefits, and alternatives, which include no intervention.

**Exceptions to informed consent**

1. Patient lacks decision-making capacity (not legally competent)
2. Implied consent in an emergency
3. Therapeutic privilege—withholding information when disclosure would severely harm the patient or undermine informed decision-making capacity
4. Waiver—patient waives the right of informed consent

**Decision-making capacity**

1. Patient makes and communicates a choice
2. Patient is informed
3. Decision remains stable over time
4. Decision is consistent with patient's values and goals
5. Decision is not a result of delusions or hallucinations

The patient's family cannot require that a doctor withhold information from the patient.

**Oral advance directive**

Incapacitated patient's prior oral statements commonly used as guide. Problems arise from variance in interpretation. If patient was informed, directive is specific, patient made a choice, and decision was repeated over time, the oral directive is more valid.

► BEHAVIORAL SCIENCE—ETHICS (*continued*)

<b>Written advance directive</b>	<p>Living will—patient directs physician to withhold or withdraw life-sustaining treatment if the patient develops a terminal disease or enters a persistent vegetative state.</p> <p>Durable power of attorney—patient designates a surrogate to make medical decisions in the event that the patient loses decision-making capacity. Patient may also specify decisions in clinical situations. Surrogate retains power unless revoked by patient. More flexible than a living will; supersedes living will if both exist.</p>	
<b>Confidentiality</b>	<p>Confidentiality respects patient privacy and autonomy. Disclosing information to family and friends should be guided by what the patient would want. The patient may also waive the right to confidentiality (e.g., insurance companies).</p>	
<b>Exceptions to confidentiality</b>	<ol style="list-style-type: none"> <li>1. Potential harm to others is serious</li> <li>2. Likelihood of harm to self is great</li> <li>3. No alternative means exist to warn or to protect those at risk</li> <li>4. Physicians can take steps to prevent harm</li> </ol> <p>Examples include:</p> <ol style="list-style-type: none"> <li>1. Infectious diseases—physicians may have a duty to warn public officials and identifiable people at risk</li> <li>2. The Tarasoff decision—law requiring physician to directly inform and protect potential victim from harm; may involve breach of confidentiality</li> <li>3. Child and/or elder abuse</li> <li>4. Impaired automobile drivers</li> <li>5. Suicidal/homicidal patient—physician may hold patient involuntarily for a period of time</li> </ol>	
<b>Malpractice</b>	<p>Civil suit under negligence requires:</p> <ol style="list-style-type: none"> <li>1. Physician had a duty to the patient (<b>D</b>uty).</li> <li>2. Physician breached that duty (<b>D</b>ereliction).</li> <li>3. Patient suffers harm (<b>D</b>amage).</li> <li>4. The breach of the duty was what caused the harm (<b>D</b>irect).</li> </ol> <p>The most common factor leading to litigation is poor communication between physician and patient.</p>	<p><b>The 4 D's.</b></p> <p>Unlike a criminal suit, in which the burden of proof is “beyond a reasonable doubt,” the burden of proof in a malpractice suit is “more likely than not.”</p>

**Ethical situations****Situation**

Patient is noncompliant.  
 Patient has difficulty taking medications.  
 Family members ask for information about patient's prognosis.  
 A 17-year-old girl is pregnant and requests an abortion.

A terminally ill patient requests physician assistance in ending his life.  
 Patient states that he finds you attractive.  
 Patient refuses a necessary procedure or desires an unnecessary one.

Patient is angry about the amount of time he spent in the waiting room.

Patient is upset with the way he was treated by another doctor.

A child wishes to know more about his illness.  
 Patient continues to smoke, believing that cigarettes are good for him.  
 Pediatric patient requests condoms.

**Appropriate response**

Work to improve the physician-patient relationship.  
 Provide written instructions; attempt to simplify treatment regimens.

Avoid discussing issues with relatives without the permission of the patient.

Many states require parental notification or consent for minors for an abortion. Parental consent is **not** required for emergency situations, treatment of STDs, medical care during pregnancy, and management of drug addiction.

In the overwhelming majority of states, refuse involvement in any form of physician-assisted suicide. Physician may, however, prescribe medically appropriate analgesics that coincidentally shorten the patient's life.

Ask direct, closed-ended questions and use a chaperone if necessary.

Romantic relationships with patients are **never** appropriate.

Attempt to understand why the patient wants/does not want the procedure. Address the underlying concerns. Avoid performing unnecessary procedures.

Apologize to the patient for any inconvenience. Stay away from efforts to explain the delay.

Suggest that the patient speak directly to that physician regarding his concerns. If the problem is with a member of the office staff, tell the patient you will speak to that individual.

Ask what the parents have told the child about his illness. Parents of a child decide what information can be relayed about the illness.

Ask how the patient feels about his smoking. Offer advice on cessation if the patient seems willing to make an effort to quit.

Physicians can provide counsel and contraceptives to minors without a parent's knowledge or consent.

**► BEHAVIORAL SCIENCE—DEVELOPMENT****APGAR Score**

A 10-point scale evaluated at 1 minute and 5 minutes.

	<b>0 points</b>	<b>1 point</b>	<b>2 points</b>
<b>Appearance</b>	Blue	Trunk pink	All pink
<b>Pulse</b>	None	< 100/min	> 100/min
<b>Grimace</b>	None	Grimace	Grimace + cough
<b>Activity</b>	Limp	Some	Active
<b>Respiration</b>	None	Irregular	Regular

► BEHAVIORAL SCIENCE—DEVELOPMENT (*continued*)

**Low birth weight** Defined as < 2500 g. Associated with greater incidence of physical and emotional problems. Caused by prematurity or intrauterine growth retardation. Complications include infections, respiratory distress syndrome, necrotizing enterocolitis, intraventricular hemorrhage, and persistent fetal circulation.

**Developmental milestones**

Approximate age	Motor milestone	Cognitive/social milestone
<b>Infant</b>		
3 mo	Holds head up, Moro reflex disappears	Social smile
4–5 mo	Rolls front to back, sits when propped	Recognizes people
7–9 mo	Sits alone, crawls	Stranger anxiety, orients to voice
12–14 mo	Upgoing Babinski disappears	
15 mo	Walks	Few words, separation anxiety
<b>Toddler</b>		
12–24 mo	Climbs stairs, stacks 3 blocks	Object permanence
18–24 mo	Stacks 6 blocks	Rapprochement
24–48 mo		Parallel play
24–36 mo		Core gender identity
<b>Preschool</b>		
30–36 mo	Stacks 9 blocks	Toilet training
3 yrs	Rides tricycle, copies line or circle drawing	Group play
4 yrs	Simple drawings (stick figure), hops on 1 foot	Cooperative play, imaginary friends, grooms self, brushes teeth
<b>School age</b>		
6–11 yrs	Reads; understands death	Development of conscience (superego), same-sex friends, identification with same-sex parent
<b>Adolescence (puberty)</b>		
11 yrs (girls)		Abstract reasoning (formal operations), formation of personality
13 yrs (boys)		

<b>Changes in the elderly</b>	1. Sexual changes—sexual interest does not ↓ Men: slower erection/ejaculation, longer refractory period Women: vaginal shortening, thinning, and dryness	Additional changes with aging: 1. ↓ vision, hearing, immune response, bladder control 2. ↓ renal, pulmonary, GI function 3. ↓ muscle mass, ↑ fat Intelligence does not ↓.
	2. Sleep patterns—↓ REM sleep, ↓ slow-wave sleep, ↑ sleep latency, ↑ awakenings during the night 3. Common medical conditions—arthritis, hypertension, heart disease, osteoporosis 4. Psychiatric problems (e.g., depression) become more prevalent 5. ↑ suicide rate	

**Tanner stages of sexual development**

1. Childhood.
2. Pubic hair begins to develop, ↑ testes size, breast tissue elevation.
3. ↑ Pubic hair, darkens, becomes curly, ↑ penis size/length.
4. ↑ Penis width, darker scrotal skin, development of glans, raised areola.
5. Adult, areola is no longer raised.

**Grief**

Normal bereavement characterized by shock, denial, guilt, and somatic symptoms. Typically lasts 6 months to 1 year. May experience illusions. Pathologic grief includes excessively intense or prolonged grief or grief that is delayed, inhibited, or denied. May experience depressive symptoms, delusions, and hallucinations.

**Kübler-Ross grief stages**

Denial, Anger, Bargaining, Grieving, Acceptance. Stages do not necessarily occur in this order, and > 1 stage can be present at once.

Death Arrives Bringing Grave Adjustments.

► **BEHAVIORAL SCIENCE—PHYSIOLOGY****Stress effects**

Stress induces production of free fatty acids, 17-OH corticosteroids, lipids, cholesterol, catecholamines; affects water absorption, muscular tonicity, gastrocolic reflex, and mucosal circulation.

**Sexual dysfunction**

Differential diagnosis includes:

1. Drugs (e.g., antihypertensives, neuroleptics, SSRIs, ethanol)
2. Diseases (e.g., depression, diabetes)
3. Psychological (e.g., performance anxiety)

**Body-mass index (BMI)**

BMI is a measure of weight adjusted for height.

$$\text{BMI} = \frac{\text{weight in kg}}{(\text{height in meters})^2}$$

< 18.5 underweight;  
18.5–24.9 normal;  
25.0–29.9 overweight;  
> 30.0 obese.

► BEHAVIORAL SCIENCE—PHYSIOLOGY (*continued*)**Sleep stages**

Stage (% of total sleep time in young adults)	Description	EEG Waveform
	Awake (eyes open), alert, active mental concentration	Beta (highest frequency, lowest amplitude)
	Awake (eyes closed)	Alpha
1 (5%)	Light sleep	Theta
2 (45%)	Deeper sleep	Sleep spindles and K complexes
3–4 (25%)	Deepest, non-REM sleep; sleepwalking; night terrors, bed-wetting (slow-wave sleep)	Delta (lowest frequency, highest amplitude)
REM (25%)	Dreaming, loss of motor tone, possibly a memory processing function, erections, ↑ brain O <sub>2</sub> use	Beta At night, <b>BATS Drink Blood</b> .
<ol style="list-style-type: none"> <li>1. Serotonergic predominance of raphe nucleus key to initiating sleep</li> <li>2. NE reduces REM sleep</li> <li>3. Extraocular movements during REM due to activity of PPRF (paramedian pontine reticular formation/conjugate gaze center)</li> <li>4. REM sleep having the same EEG pattern as while awake and alert has spawned the terms “paradoxical sleep” and “desynchronized sleep”</li> <li>5. Benzodiazepines shorten stage 4 sleep; thus useful for night terrors and sleepwalking</li> <li>6. Imipramine is used to treat enuresis because it ↓ stage 4 sleep</li> </ol>		
<b>REM sleep</b>	↑ and variable pulse, REM, ↑ and variable blood pressure, penile/clitoral tumescence. Occurs every 90 minutes; duration ↑ through the night. ACh is the principal neurotransmitter involved in REM sleep. REM sleep ↓ with age.	REM sleep is like sex: ↑ pulse, penile/clitoral tumescence, ↓ with age.
<b>Narcolepsy</b>	Disordered regulation of sleep-wake cycles. May include hypnagogic (just before sleep) or hypnopompic (just before awakening) hallucinations. The patient's nocturnal and narcoleptic sleep episodes start off with REM sleep. <b>Cataplexy</b> (loss of all muscle tone following a strong emotional stimulus) in some patients. Strong genetic component. Treat with stimulants (e.g., amphetamines).	

## ► BEHAVIORAL SCIENCE—PSYCHOLOGY

**Intelligence quotient**

Stanford-Binet and Wechsler are the most famous tests of intelligence quotient (IQ). Stanford-Binet calculates IQ as mental age/chronological age × 100. Wechsler Adult Intelligence Scale uses 11 subtests (6 verbal, 5 performance). Mean is defined at 100, with standard deviation of 15. IQ < 70 (or 2 standard deviations below the mean) is one of the criteria for diagnosis of mental retardation (MR). IQ < 40—severe MR. IQ < 20—profound MR. IQ scores are correlated with genetic factors and are highly correlated with school achievement. Intelligence tests are objective (not projective) tests.

<b>Classical conditioning</b>	Learning in which a natural response (salivation) is elicited by a conditioned, or learned, stimulus (bell) that previously was presented in conjunction with an unconditioned stimulus (food).	Pavlov's classical experiments with dogs—ringing the bell provoked salivation.
<b>Operant conditioning</b>	Learning in which a particular action is elicited because it produces a reward. Positive reinforcement—desired reward produces action (mouse presses button to get food). Negative reinforcement—removal of aversive stimulus ↑ behavior (mouse presses button to avoid shock). Do not confuse with punishment.	
<b>Reinforcement schedules</b>	Pattern of reinforcement determines how quickly a behavior is learned or extinguished.	
Continuous	Reward received after every response. Rapidly extinguished.	Think vending machine—stop using it if it does not deliver.
Variable ratio	Reward received after random number of responses. Slowly extinguished.	Think slot machine—continue to play even if it rarely rewards.
<b>Transference and countertransference</b>		
Transference	Patient projects feelings about formative or other important persons onto physician (e.g., psychiatrist = parent).	
Countertransference	Doctor projects feelings about formative or other important persons onto patient.	
<b>Structural theory of the mind</b>	Freud's 3 structures of the mind.	
Id	Primal urges, sex, and aggression. (I want it.)	
Ego	Mediator between the unconscious mind and the external world. (Deals with the conflict. Take it and you will get in trouble.)	
Superego	Moral values, conscience. (You know you can't have it. Taking it is wrong.)	
<b>Topographic theory of the mind</b>	Conscious—what you are aware of. Preconscious—what you are able to make conscious with effort (e.g., your phone number). Unconscious—what you are not aware of; the central goal of Freudian psychoanalysis is to make the patient aware of what is hidden in his/her unconscious.	
<b>Oedipus complex</b>	Repressed sexual feelings of a child for the opposite-sex parent, accompanied by rivalry with same-sex parent. First described by Freud.	

► BEHAVIORAL SCIENCE—PSYCHOLOGY (*continued*)

<b>Ego defenses</b>	All ego defenses are automatic and unconscious reactions to psychological stress.	
<b>Mature</b>		
Altruism	Guilty feelings alleviated by unsolicited generosity toward others.	Mafia boss makes large donation to charity.
Humor	Appreciating the amusing nature of an anxiety-provoking or adverse situation.	Nervous medical student jokes about the boards.
Sublimation	Process whereby one replaces an unacceptable wish with a course of action that is similar to the wish but does not conflict with one's value system.	Aggressive impulses used to succeed in business ventures.
Suppression	Voluntary (unlike repression) withholding of an idea or feeling from conscious awareness.	Choosing not to think about the USMLE until the week of the exam.
	<b>Mature</b> women wear a <b>SASH</b> : Sublimation, Altruism, Suppression, Humor.	
<b>Immature</b>		
Acting out	Unacceptable feelings and thoughts are expressed through actions.	Tantrums.
Dissociation	Temporary, drastic change in personality, memory, consciousness, or motor behavior to avoid emotional stress.	Extreme forms can result in multiple personalities (dissociative identity disorder).
Denial	Avoidance of awareness of some painful reality.	A common reaction in newly diagnosed AIDS and cancer patients.
Displacement	Process whereby avoided ideas and feelings are transferred to some neutral person or object.	Mother yells at child because she is angry at her husband.
Fixation	Partially remaining at a more childish level of development.	Men fixating on sports games.
Identification	Modeling behavior after another person who is more powerful (though not necessarily admired).	Abused child becomes an abuser.
Isolation	Separation of feelings from ideas and events.	Describing murder in graphic detail with no emotional response.
Projection	An unacceptable internal impulse is attributed to an external source.	A man who wants another woman thinks his wife is cheating on him.
Rationalization	Proclaiming logical reasons for actions actually performed for other reasons, usually to avoid self-blame.	Saying the job was not important anyway, after getting fired.
Reaction formation	Process whereby a ward-off idea or feeling is replaced by an (unconsciously derived) emphasis on its opposite.	A patient with libidinous thoughts enters a monastery.
Regression	Turning back the maturational clock and going back to earlier modes of dealing with the world.	Seen in children under stress (e.g., bed-wetting) and in patients on dialysis (e.g., crying).
Repression	Involuntary withholding of an idea or feeling from conscious awareness. The basic mechanism underlying all others.	
Splitting	Belief that people are either all good or all bad.	A patient says that all the nurses are cold and insensitive but that the doctors are warm and friendly.



# HIGH-YIELD PRINCIPLES IN

# Biochemistry

*“Biochemistry is the study of carbon compounds that crawl.”*

—Mike Adams

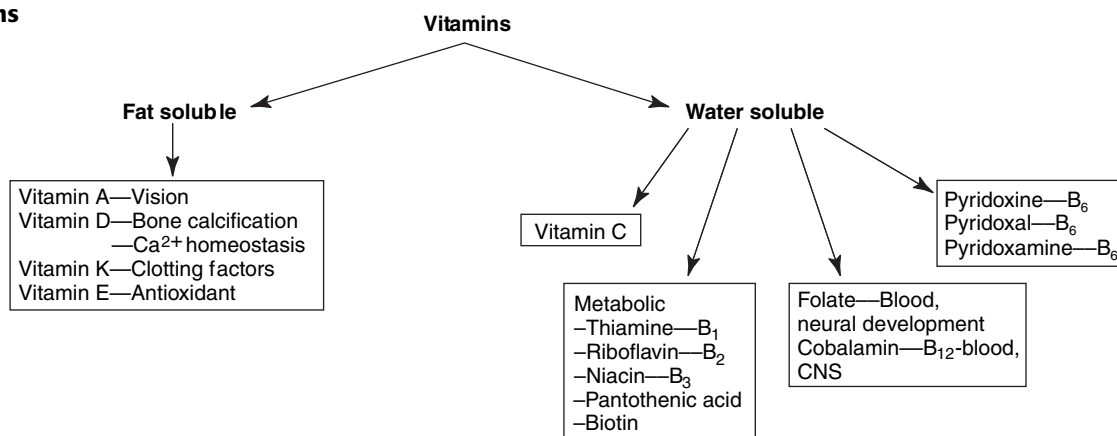
This high-yield material includes molecular biology, genetics, cell biology, and principles of metabolism (especially vitamins, cofactors, minerals, and single-enzyme-deficiency diseases). When studying metabolic pathways, emphasize important regulatory steps and enzyme deficiencies that result in disease. For example, understanding the defect in Lesch-Nyhan syndrome and its clinical consequences is higher yield than memorizing every intermediate in the purine salvage pathway. Do not spend time on hard-core organic chemistry, mechanisms, and physical chemistry. Detailed chemical structures are infrequently tested. Familiarity with the latest biochemical techniques that have medical relevance—such as enzyme-linked immunosorbent assay (ELISA), immunoelectrophoresis, Southern blotting, and PCR—is useful. Beware if you placed out of your medical school’s biochemistry class, for the emphasis of the test differs from that of many undergraduate courses. Review the related biochemistry when studying pharmacology or genetic diseases as a way to reinforce and integrate the material.

- ▶ High-Yield Clinical Vignettes
- ▶ Nutrition
- ▶ Molecular
- ▶ Cellular
- ▶ Metabolism
- ▶ Laboratory Techniques
- ▶ Genetics

## BIOCHEMISTRY—HIGH-YIELD CLINICAL VIGNETTES

■ Full-term neonate of uneventful delivery becomes mentally retarded and hyperactive and has a musty odor.	What is the diagnosis?	PKU.
■ Stressed executive comes home from work, consumes 7 or 8 martinis in rapid succession before dinner, and becomes hypoglycemic.	What is the mechanism?	NADH increase prevents gluconeogenesis by shunting pyruvate and oxaloacetate to lactate and malate.
■ 2-year-old girl has an ↑ in abdominal girth, failure to thrive, and skin and hair depigmentation.	What is the diagnosis?	Kwashiorkor.
■ Alcoholic develops a rash, diarrhea, and altered mental status.	What is the vitamin deficiency?	Vitamin B <sub>3</sub> (pellagra).
■ 51-year-old man has black spots in his sclera and has noted that his urine turns black upon standing.	What is the diagnosis?	Alkaptonuria.
■ 25-year-old male complains of severe chest pain and has xanthomas of his Achilles tendons.	What is the disease, and where is the defect?	Familial hypercholesterolemia; LDL receptor.
■ A woman complains of intense muscle cramps and darkened urine after exercise.	What is the diagnosis?	McArdle's disease.
■ Two parents with albinism have a son who is normal.	Why is the son not affected?	Locus heterogeneity.
■ A 40-year-old man has chronic pancreatitis with pancreatic insufficiency.	What vitamins are likely deficient?	A, D, E, and K.

## Vitamins



### Vitamins: fat soluble

A, D, E, K. Absorption dependent on gut (ileum) and pancreas. Toxicity more common than for water-soluble vitamins, because these accumulate in fat.

Malabsorption syndromes (steatorrhea), such as cystic fibrosis and sprue, or mineral oil intake can cause fat-soluble vitamin deficiencies.

### Vitamins: water soluble

B<sub>1</sub> (thiamine: TPP)  
B<sub>2</sub> (riboflavin: FAD, FMN)  
B<sub>3</sub> (niacin: NAD<sup>+</sup>)  
B<sub>5</sub> (pantothenate: CoA)  
B<sub>6</sub> (pyridoxine: PP)  
B<sub>12</sub> (cobalamin)  
C (ascorbic acid)  
Biotin  
Folate

All wash out easily from body except B<sub>12</sub> (stored in liver). B-complex deficiencies often result in dermatitis, glossitis, and diarrhea.

### Vitamin A (retinol)

Deficiency: Night blindness, dry skin.

Function: Constituent of visual pigments (retinal).

Excess: Arthralgias, fatigue, headaches, skin changes, sore throat, alopecia.

**Retinol** is vitamin **A**, so think **Retin-A** (used topically for wrinkles and acne). Found in leafy vegetables.

### Vitamin B<sub>1</sub> (thiamine)

Deficiency: Beriberi and Wernicke-Korsakoff syndrome. Seen in alcoholism and malnutrition.

Function: In thiamine pyrophosphate, a cofactor for oxidative decarboxylation of  $\alpha$ -keto acids (pyruvate,  $\alpha$ -ketoglutarate) and a cofactor for transketolase in the HMP shunt.

Spell beriberi as **Ber1Ber1**. Dry beriberi—polyneuritis, muscle wasting. Wet beriberi—high-output cardiac failure (dilated cardiomyopathy), edema.

► BIOCHEMISTRY–NUTRITION (*continued*)**Vitamin B<sub>2</sub> (riboflavin)**

Deficiency	Angular stomatitis, Cheilosis, Corneal vascularization.	The 2 C's.
Function	Cofactor in oxidation and reduction (e.g., FADH <sub>2</sub> ).	FAD and FMN are derived from riboFlavin (B <sub>2</sub> = 2 ATP).

**Vitamin B<sub>3</sub> (niacin)**

Deficiency	Pellagra can be caused by Hartnup disease (↓ tryptophan absorption), malignant carcinoid syndrome (↑ tryptophan metabolism), and INH (↓ vitamin B <sub>6</sub> ).	Pellagra's symptoms are the 3 D's: Diarrhea, Dermatitis, Dementia (also beefy glossitis).
Function	Constituent of NAD <sup>+</sup> , NADP <sup>+</sup> (used in redox reactions). Derived from tryptophan using vitamin B <sub>6</sub> .	NAD derived from Niacin (B <sub>3</sub> = 3 ATP).

**Vitamin B<sub>5</sub> (pantothenate)**

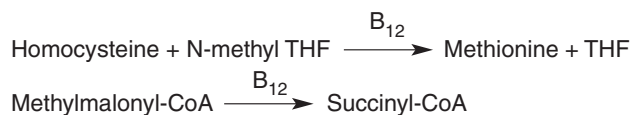
Deficiency	Dermatitis, enteritis, alopecia, adrenal insufficiency.	
Function	Constituent of CoA (a cofactor for acyl transfers) and component of fatty acid synthase.	Pantothen-A is in Co-A.

**Vitamin B<sub>6</sub> (pyridoxine)**

Deficiency	Convulsions, hyperirritability (deficiency inducible by INH and oral contraceptives), peripheral neuropathy.	
Function	Converted to pyridoxal phosphate, a cofactor used in transamination (e.g., ALT and AST), decarboxylation, and heme synthesis.	

**Vitamin B<sub>12</sub> (cobalamin)**

Deficiency	Macrocytic, megaloblastic anemia; neurologic symptoms (optic neuropathy, subacute combined degeneration, paresthesia); glossitis.	Found only in animal products. Vitamin B <sub>12</sub> deficiency is usually caused by malabsorption (sprue, enteritis, <i>Diphyllobothrium latum</i> ), lack of intrinsic factor (pernicious anemia), or absence of terminal ileum (Crohn's disease).
Function	Cofactor for homocysteine methylation (transfers CH <sub>3</sub> groups as methylcobalamin) and methylmalonyl-CoA handling. Stored primarily in the liver. Very large reserve pool (several years). Synthesized only by microorganisms.	Use Schilling test to detect deficiency. Abnormal myelin is seen in B <sub>12</sub> deficiency, possibly due to ↓ methionine or ↑ methylmalonic acid (from metabolism of accumulated methylmalonyl-CoA).



<b>Folic acid</b>		
Deficiency	Most common vitamin deficiency in the United States. Macrocytic, megaloblastic anemia (often no neurologic symptoms, as opposed to vitamin B <sub>12</sub> deficiency).	<b>FOL</b> ate from <b>FOL</b> iage. Eat green leaves (because folic acid is not stored very long). Supplemental folic acid in early pregnancy reduces neural tube defects.
Function	Coenzyme (tetrahydrofolate) for 1-carbon transfer; involved in methylation reactions. Important for the synthesis of nitrogenous bases in DNA and RNA.	PABA is the folic acid precursor in bacteria. Sulfonamides (antimicrobials) are PABA analogs.
<hr/>		
<b>Biotin</b>		
Deficiency	Dermatitis, enteritis. Caused by antibiotic use, ingestion of raw eggs.	“ <b>AVID</b> in in egg whites <b>AVID</b> ly binds biotin.”
Function	Cofactor for carboxylations: 1. Pyruvate → oxaloacetate 2. Acetyl-CoA → malonyl-CoA 3. Propionyl-CoA → methylmalonyl-CoA	
<hr/>		
<b>Vitamin C (ascorbic acid)</b>		
Deficiency	Scurvy—swollen gums, bruising, anemia, poor wound healing.	Vitamin C Cross-links Collagen. British sailors carried limes to prevent scurvy (origin of the word “limey”).
Function	Necessary for hydroxylation of proline and lysine in collagen synthesis. Facilitates iron absorption by keeping iron in Fe <sup>+2</sup> reduced state (more absorbable) Necessary as a cofactor for dopamine → NE.	
<hr/>		
<b>Vitamin D</b>		
	D <sub>2</sub> = ergocalciferol, consumed in milk. D <sub>3</sub> = cholecalciferol, formed in sun-exposed skin. 25-OH D <sub>3</sub> = storage form. 1,25 (OH) <sub>2</sub> D <sub>3</sub> = active form.	Remember that drinking milk (fortified with vitamin D) is good for bones.
Deficiency	Rickets in children (bending bones), osteomalacia in adults (soft bones), and hypocalcemic tetany.	
Function	↑ intestinal absorption of calcium and phosphate.	
Excess	Hypercalcemia, loss of appetite, stupor. Seen in sarcoidosis, a disease where the epithelioid macrophages convert vitamin D into its active form.	
<hr/>		
<b>Vitamin E</b>		
Deficiency	Increased fragility of erythrocytes, neurodysfunction.	Vitamin E is for Erythrocytes.
Function	Antioxidant (protects erythrocytes from hemolysis).	

► BIOCHEMISTRY–NUTRITION (*continued*)**Vitamin K**

Deficiency

Neonatal hemorrhage with ↑ PT and ↑ aPTT but normal bleeding time, because neonates have sterile intestines and are unable to synthesize vitamin K.

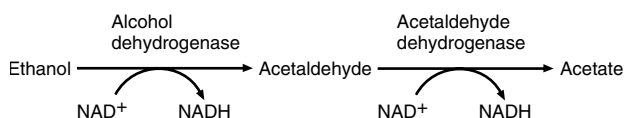
**K** for **K**oagulation. Note that the vitamin K–dependent clotting factors are II, VII, IX, X, and protein C and S. Warfarin is a vitamin K antagonist.

Function

Catalyzes  $\gamma$ -carboxylation of glutamic acid residues on various proteins concerned with blood clotting. Synthesized by intestinal flora. Therefore, vitamin K deficiency can occur after the prolonged use of broad-spectrum antibiotics.

**Zinc deficiency**

Delayed wound healing, hypogonadism, ↓ adult hair (axillary, facial, pubic); may predispose to alcoholic cirrhosis.

**Ethanol metabolism**

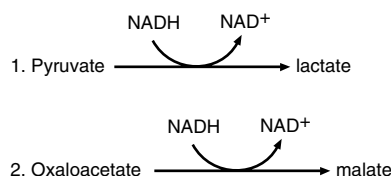
Disulfiram (Antabuse) inhibits acetaldehyde dehydrogenase (acetaldehyde accumulates, contributing to hangover symptoms).

NAD<sup>+</sup> is the limiting reagent.

Alcohol dehydrogenase operates via zero-order kinetics.

**Ethanol hypoglycemia**

Ethanol metabolism ↑ NADH/NAD<sup>+</sup> ratio in liver, causing diversion of pyruvate to lactate and OAA to malate, thereby inhibiting gluconeogenesis and leading to hypoglycemia. This altered NADH/NAD<sup>+</sup> ratio is responsible for the hepatic fatty change (hepatocellular steatosis) seen in chronic alcoholics (shunting away from glycolysis and toward fatty acid synthesis).

**Kwashiorkor vs. marasmus**

Kwashiorkor—protein malnutrition resulting in skin lesions, edema, liver malfunction (fatty change). Clinical picture is small child with swollen belly.  
Marasmus—energy malnutrition resulting in tissue and muscle wasting, loss of subcutaneous fat, and variable edema.

Kwashiorkor results from a protein-deficient **MEAL**:  
**M**alabsorption  
**E**dema  
**A**nemia  
**L**iver (fatty)

**Chromatin structure**

(-) charged DNA loops twice around nucleosome core (2 each of the (+) charged H2A, H2B, H3, and H4) to form nucleosome bead.

Think of beads on a string.

H1 ties nucleosomes together in a string (30-nm fiber).

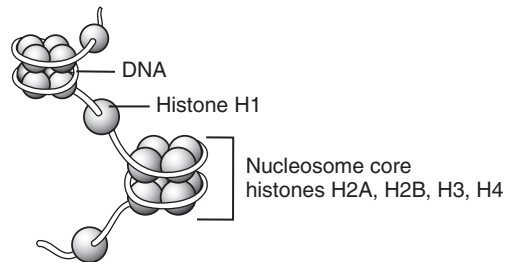
H1 is the only histone that is not in the nucleosome core.

In mitosis, DNA condenses to form mitotic chromosomes.

Heterochromatin  
Euchromatin

Condensed, transcriptionally inactive.  
Less condensed, transcriptionally active.

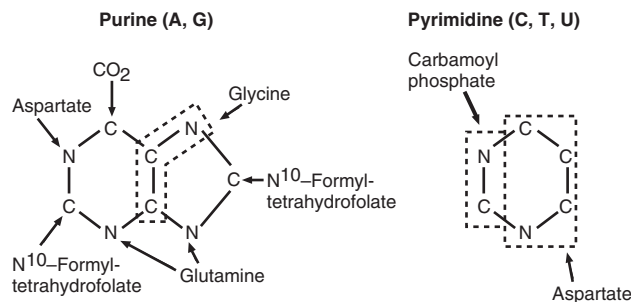
*Eu* = true, "truly transcribed."



**Nucleotides**

Purines (A, G) have 2 rings. Pyrimidines (C, T, U) have 1 ring. Guanine has a ketone. Thymine has a methyl. Deamination of cytosine makes uracil. Uracil found in RNA; thymine in DNA. G-C bond (3 H-bonds) stronger than A-T bond (2 H-bonds). ↑ G-C content → ↑ melting temperature.

**PUR**e As Gold: **PUR**ines.  
**CUT** the **PY** (pie):  
**PY**rimidines.  
**THY**mine has a me**THY**L.



Amino acids necessary for purine synthesis:  
Glycine  
Aspartate  
Glutamine

Nucleotides (base + ribose + phosphate) are linked by 3'-5' phosphodiester bond.

**Transition vs. transversion**

Transition Substituting purine for purine or pyrimidine for pyrimidine.  
Transversion Substituting purine for pyrimidine or visa versa.

Trans**I**tion = **I**dentical type.  
Trans**V**ersion = con**V**ersion between types.

► BIOCHEMISTRY—MOLECULAR (*continued*)**Genetic code features**

Unambiguous	Each codon specifies only one amino acid.	
Degenerate/redundant	More than one codon may code for the same amino acid.	Methionine encoded by only one codon.
Commaless, nonoverlapping	Read from a fixed starting point as a continuous sequence of bases.	Some viruses are an exception.
Universal	Genetic code is conserved throughout evolution.	Exceptions include mitochondria, archaeobacteria, <i>Mycoplasma</i> , and some yeasts.

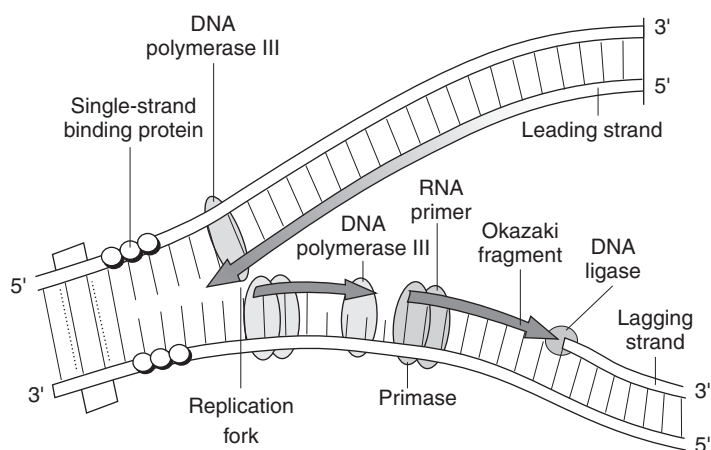
**Mutations in DNA**

Silent	Same aa, often base change in 3rd position of codon (tRNA wobble).	Severity of damage: nonsense > missense > silent.
Missense	Changed aa (conservative—new aa is similar in chemical structure).	
Nonsense	Change resulting in early <b>stop</b> codon.	<b>Stop the nonsense!</b>
Frame shift	Change resulting in misreading of all nucleotides downstream, usually resulting in a truncated protein.	



**DNA replication and DNA polymerases**

<b>Eukaryotes</b>	Eukaryotic genome has multiple origins of replication. Replication begins at a consensus sequence of AT-rich base pairs.	
<b>Prokaryotes</b>	Single origin of replication—continuous bidirectional DNA synthesis on leading strand and discontinuous (Okazaki fragments) on lagging strand.	
<b>DNA topoisomerases</b>	Create a nick in the helix to relieve supercoils.	
<b>Primase</b>	Makes an RNA <b>primer</b> on which DNA polymerase III can initiate replication.	
<b>DNA polymerase III</b>	Elongates the chain by adding deoxynucleotides to the 3' end until it reaches primer of preceding fragment. 3' → 5' exonuclease activity “proofreads” each added nucleotide.	DNA polymerase III has 5' → 3' synthesis and proofreads with 3' → 5' exonuclease.
<b>DNA polymerase I</b>	Degrades RNA primer and fills in the gap with DNA.	DNA polymerase I excises RNA primer with 5' → 3' exonuclease.
<b>DNA ligase</b>	Seals.	



► BIOCHEMISTRY—MOLECULAR (*continued*)**DNA repair****Single strand**

Nucleotide excision repair

Specific endonucleases release the oligonucleotide-containing damaged bases; DNA polymerase and ligase fill and reseal the gap, respectively.

Mutated in **xeroderma pigmentosa** (dry skin with melanoma and other cancers).

Base excision repair

Specific glycosylases recognize and remove damaged bases, AP endonuclease cuts DNA at apyrimidinic site, empty sugar is removed, and the gap is filled and resealed.

Mismatch repair

Unmethylated, newly synthesized string is recognized, mismatched nucleotides are removed, and the gap is filled and resealed.

Mutated in **hereditary nonpolyposis colon cancer**.**Double strand**

Nonhomologous end joining

Brings together two ends of DNA fragments.  
No requirement for homology.**DNA/RNA/protein synthesis direction**DNA and RNA are both synthesized **5' → 3'**.  
Remember that the 5' of the incoming nucleotide bears the triphosphate (energy source for bond).  
The 3' hydroxyl of the nascent chain is the target.Protein synthesis also proceeds in the 5' to 3' direction.  
Amino acids are linked N to C.**Types of RNA****mRNA** is the **largest** type of RNA.  
**rRNA** is the most **abundant** type of RNA.  
**tRNA** is the **smallest** type of RNA.**Massive, Rampant, Tiny.****RNA polymerases**

Eukaryotes

RNA polymerase I makes **rRNA**.  
RNA polymerase II makes **mRNA**.  
RNA polymerase III makes **tRNA**.  
No proofreading function, but can initiate chains.  
RNA polymerase II opens DNA at promoter site  
**α-amanitin** inhibits RNA polymerase II.

I, II, and III are numbered as their products are used in protein synthesis.

Prokaryotes

RNA polymerase (multisubunit complex) makes all 3 kinds of RNA.

**α-amanitin** is found in death cap mushrooms.**Start and stop codons****mRNA initiation codons**

AUG (or rarely GUG).

**AUG** **in** **AUG**urates protein synthesis.

Eukaryotes

Codes for methionine, which may be removed before translation is completed.

Prokaryotes

Codes for formyl-methionine (f-Met).

**mRNA stop codons**

UGA, UAA, UAG.

**UGA = U Go Away.**  
**UAA = U Are Away.**  
**UAG = U Are Gone.**

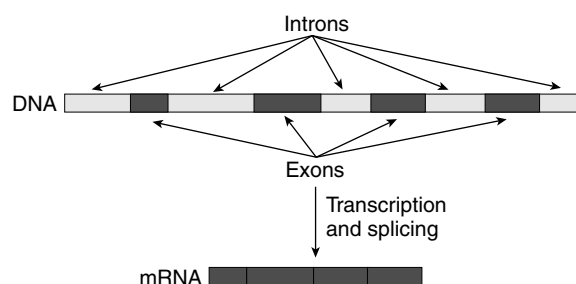
### Regulation of gene expression

Promoter	Site where RNA polymerase and multiple other transcription factors bind to DNA upstream from gene locus (AT-rich upstream sequence with TATA and CAAT boxes).	Promoter mutation commonly results in dramatic ↓ in amount of gene transcribed.
Enhancer	Stretch of DNA that alters gene expression by binding transcription factors. May be located close to, far from, or even within (in an intron) the gene whose expression it regulates.	
Operator	Site where negative regulators (repressors) bind.	

### Introns vs. exons

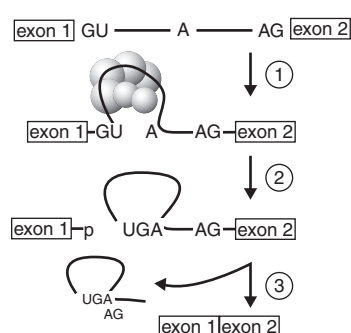
Exons contain the actual genetic information coding for protein.  
Introns are intervening noncoding segments of DNA.

**IN**trons stay **IN** the nucleus, whereas **EX**ons **EX**it and are **EX**pressed.



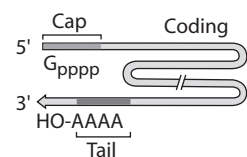
Different exons can be combined by **alternative splicing** to make unique proteins in different tissues.

### Splicing of mRNA



- ① Primary transcript combines with snRNPs to form spliceosome.
- ② Lariat-shaped intermediate is generated.
- ③ Lariat is released to remove intron precisely and join two exons.

### RNA processing (eukaryotes)



Occurs in nucleus. After transcription:

1. Capping on 5' end (7-methyl-G)
2. Polyadenylation on 3' end ( $\approx 200$  A's)
3. Splicing out of introns

Initial transcript is called heterogeneous nuclear RNA (hnRNA).

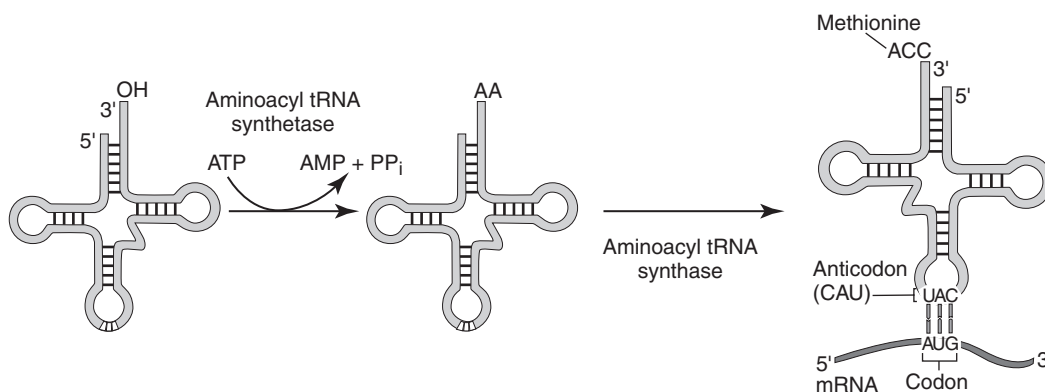
Capped and tailed transcript is called mRNA.

Only processed RNA is transported out of the nucleus.

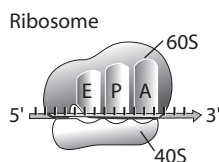
## ► BIOCHEMISTRY—MOLECULAR (continued)

**tRNA**

<b>Structure</b>	75–90 nucleotides, cloverleaf form, anticodon end is opposite 3' aminoacyl end. All tRNAs, both eukaryotic and prokaryotic, have CCA at 3' end along with a high percentage of chemically modified bases. The amino acid is covalently bound to the 3' end of the tRNA.	
<b>Charging</b>	Aminoacyl-tRNA synthetase (1 per aa, uses ATP) scrutinizes aa before and after it binds to tRNA. If incorrect, bond is hydrolyzed by synthetase. The aa-tRNA bond has energy for formation of peptide bond. A mischarged tRNA reads usual codon but inserts wrong amino acid.	Aminoacyl-tRNA synthetase and binding of charged tRNA to the codon are responsible for accuracy of amino acid selection.

**tRNA wobble**

Accurate base pairing is required only in the first 2 nucleotide positions of an mRNA codon, so codons differing in the 3rd “wobble” position may code for the same tRNA/amino acid.

**Protein synthesis**

<b>Initiation</b>	Initiation factors (IFs) help assemble the 30S ribosomal subunit with the initiator tRNA, are released when the mRNA and the ribosomal subunit assemble with the complex.	ATP—tRNA Activation (charging). GTP—tRNA Gripping and Going places (translocation).
<b>Elongation</b>	<ol style="list-style-type: none"> <li>1. Aminoacyl tRNA binds to A site.</li> <li>2. Peptidyltransferase catalyzes peptide bond formation, transfers growing polypeptide to amino acid in A site.</li> <li>3. Ribosome advances three nucleotides toward 3' end of RNA, moving peptidyl RNA to P site.</li> </ol>	A site = incoming Aminoacyl tRNA. P site = accommodates growing Peptide. E site = holds Empty tRNA as it Exits.
<b>Termination</b>	Completed protein is released from ribosome, which dissociates.	

**Posttranslational modifications**

Trimming	Removal of N- or C-terminal pro-peptides from zymogens to generate mature proteins.
Covalent alterations	Phosphorylation, glycosylation, and hydroxylation.
Proteasomal degradation	Attachment of ubiquitin to defective proteins to tag them for breakdown.

**► BIOCHEMISTRY—CELLULAR****Enzyme regulation methods**

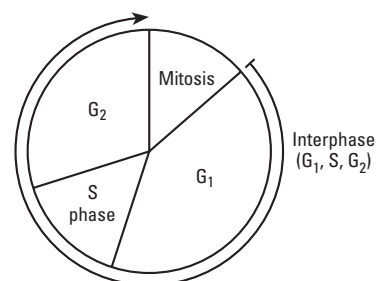
Enzyme concentration alteration (synthesis and/or destruction), covalent modification (e.g., phosphorylation), proteolytic modification (zymogen), allosteric regulation (e.g., feedback inhibition), pH, temperature, and transcriptional regulation (e.g., steroid hormones).

**Cell cycle phases**

Checkpoints control transitions between phases. Regulated by cyclins, cdks, and tumor suppressors.

Mitosis (shortest phase): prophase-metaphase-anaphase-telophase.  $G_1$  and  $G_0$  are of variable duration.

G stands for Gap or Growth; S for Synthesis.



Permanent cells

Remain in  $G_0$ , regenerate from stem cells.

Neurons, skeletal and cardiac muscle, RBCs.

Stable cells

Enter  $G_1$  from  $G_0$  when stimulated.

Hepatocytes, lymphocytes.

Labile cells

Never go to  $G_0$ , divide rapidly with a short  $G_1$ .

Bone marrow, gut epithelium, skin, hair follicles.

**Rough endoplasmic reticulum (RER)**

RER is the site of synthesis of secretory (exported) proteins and of N-linked oligosaccharide addition to many proteins.

Mucus-secreting goblet cells of the small intestine and antibody-secreting plasma cells are rich in RER.

Nissl bodies (in neurons)—synthesize enzymes (e.g., ChAT) and peptide neurotransmitters.

**Smooth endoplasmic reticulum (SER)**

SER is the site of steroid synthesis and detoxification of drugs and poisons.

Liver hepatocytes and steroid hormone-producing cells of the adrenal cortex are rich in SER.

► BIOCHEMISTRY—CELLULAR (*continued*)**Functions of Golgi apparatus**

1. Distribution center of proteins and lipids from ER to the plasma membrane, lysosomes, and secretory vesicles
2. Modifies N-oligosaccharides on asparagine
3. Adds O-oligosaccharides to serine and threonine residues
4. Addition of mannose-6-phosphate to specific lysosomal proteins, which targets the protein to the lysosome
5. Proteoglycan assembly from proteoglycan core proteins
6. Sulfation of sugars in proteoglycans and of selected tyrosine on proteins

**I-cell disease:** failure of addition of mannose-6-phosphate to lysosome proteins, enzymes are secreted outside the cell instead of being targeted to the lysosome.

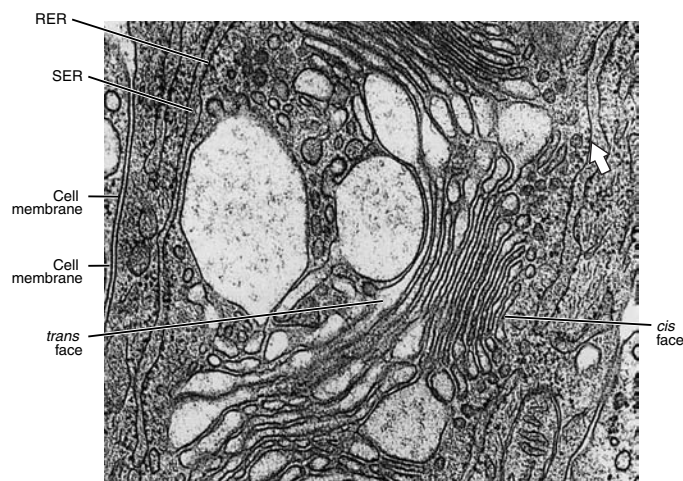
Characterized by coarse facial features, clouded corneas, restricted joint movement, and high plasma levels of lysosomal enzymes. Often fatal in childhood.

**Vesicular trafficking proteins:**

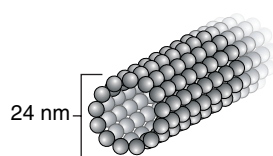
COPI: Retrograde,  
Golgi → ER.

COPII: Anterograde,  
RER → cis-Golgi.

Clathrin: trans-Golgi →  
lysosomes, plasma  
membrane → endosomes  
(receptor-mediated  
endocytosis).



(Reproduced, with permission, from Junqueira L, Carneiro J. *Basic Histology*, 10th ed. New York:McGraw-Hill, 2003.)

**Microtubule**

Cylindrical structure 24 nm in diameter and of variable length. A helical array of polymerized dimers of  $\alpha$ - and  $\beta$ -tubulin (13 per circumference). Each dimer has 2 GTP bound. Incorporated into flagella, cilia, mitotic spindles. Grows slowly, collapses quickly. Microtubules are also involved in slow axoplasmic transport in neurons.

**Drugs that act on microtubules:**

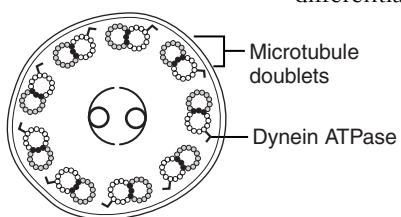
1. Mebendazole/thiabendazole (anthelmintic)
2. Taxol (anti-breast cancer)
3. Griseofulvin (antifungal)
4. Vincristine/vinblastine (anti-cancer)
5. Colchicine (anti-gout)

**Chédiak-Higashi syndrome**

is due to a microtubule polymerization defect resulting in  $\downarrow$  phagocytosis.

**Cilia structure**

9 + 2 arrangement of microtubules. Dynein is an ATPase that links peripheral 9 doublets and causes bending of cilium by differential sliding of doublets.

**Molecular motors**

Dynein = retrograde.  
Kinesin = anterograde.

**Kartagener's syndrome**

Immotile cilia due to a dynein arm defect. Results in male and female infertility (sperm immotile), bronchiectasis, and recurrent sinusitis (bacteria and particles not pushed out); associated with situs inversus.

**Plasma membrane composition**

Asymmetric fluid bilayer.  
Contains cholesterol (~50%), phospholipids (~50%), sphingolipids, glycolipids, and proteins.  
High cholesterol or long saturated fatty acid content  $\rightarrow$  increased melting temperature.

**Phosphatidylcholine (lecithin) function**

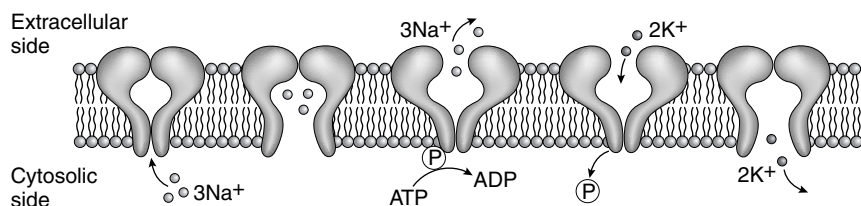
Major component of RBC membranes, of myelin, bile, and surfactant (DPPC—dipalmitoyl phosphatidylcholine).  
Used in esterification of cholesterol (LCAT is lecithin-cholesterol acyltransferase).

► BIOCHEMISTRY—CELLULAR (*continued*)**Sodium pump**

$\text{Na}^+\text{-K}^+\text{ATPase}$  is located in the plasma membrane with ATP site on cytoplasmic side. For each ATP consumed, 3  $\text{Na}^+$  go out and 2  $\text{K}^+$  come in. During cycle, pump is phosphorylated.

**Ouabain** inhibits by binding to  $\text{K}^+$  site.

**Cardiac glycosides** (digoxin, digitoxin) also inhibit the  $\text{Na}^+\text{-K}^+\text{ATPase}$ , causing  $\uparrow$  cardiac contractility.

**Collagen**

Most abundant protein in the human body. Organizes and strengthens extracellular matrix.  
 Type I (90%)—**B**one, **S**kin, **T**endon, dentin, fascia, cornea, late wound repair.  
 Type II—**C**artilage (including hyaline), vitreous body, nucleus pulposus.  
 Type III (**R**eticulin)—skin, blood vessels, uterus, fetal tissue, granulation tissue.  
 Type IV—**B**asement membrane or basal lamina.

**Be (So Totally) Cool, Read Books.**

Type I: **BONE**.

Type II: **carTWOlage**.

Type IV: **Under the floor** (basement membrane).

**Collagen synthesis and structure****Inside fibroblasts**

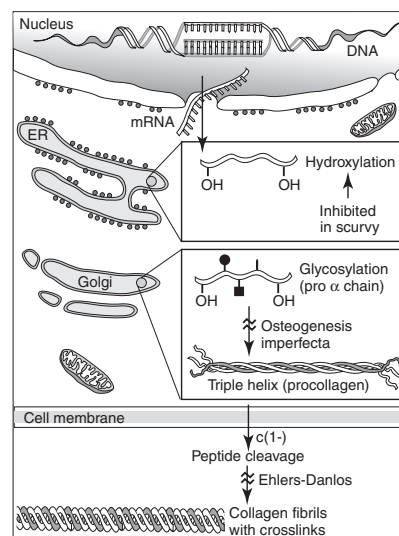
1. Synthesis (RER)
2. Hydroxylation (ER)
3. Glycosylation (Golgi)
4. Exocytosis

Translation of collagen  $\alpha$  chains (**preprocollagen**)—usually Gly-X-Y polypeptide (X and Y are proline, hydroxyproline, or hydroxylysine).  
 Hydroxylation of specific proline and lysine residues (requires **vitamin C**).  
 Glycosylation of pro- $\alpha$ -chain lysine residues and formation of **procollagen** (triple helix of three collagen  $\alpha$  chains).  
 Exocytosis of procollagen into extracellular space.

**Outside fibroblasts**

5. Proteolytic processing
6. Cross-linking

Cleavage of terminal regions of procollagen transforms it into insoluble **tropocollagen**.  
 Reinforcement of many staggered tropocollagen molecules by covalent lysine-hydroxylysine cross-linkage (by lysyl oxidase) to make **collagen fibrils**.

**Ehlers-Danlos syndrome**

Faulty collagen synthesis causing:

1. Hyperextensible skin
2. Tendency to bleed (easy bruising)
3. Hypermobility joints

10 types. Inheritance varies. Associated with berry aneurysms.

**Type III** is most frequently affected (resulting in blood vessel instability).



<b>Osteogenesis imperfecta</b>	<p>Variety of gene defects; all result in abnormal collagen synthesis.</p> <p>Most common form is autosomal-dominant with abnormal collagen type I.</p> <ol style="list-style-type: none"> <li>1. <b>Multiple fractures</b> occurring with minimal trauma (brittle bone disease), which may occur during the birth process</li> <li>2. <b>Blue sclerae</b> due to the translucency of the connective tissue over the choroid</li> <li>3. Hearing loss (abnormal middle ear bones)</li> <li>4. Dental imperfections due to lack of dentition</li> </ol>	<p>May be confused with child abuse.</p> <p>Type II is fatal in utero or in the neonatal period.</p> <p>Incidence is 1:10,000.</p>
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#### Immunohistochemical stains

Stain	Cell type
Vimentin	Connective tissue
Desmin	Muscle
Cytokeratin	Epithelial cells
Glial fibrillary acid proteins (GFAP)	Neuroglia
Neurofilaments	Neurons

<b>Elastin</b>	<p>Stretchy protein within lungs, large arteries, elastic ligaments.</p> <p>Rich in proline and lysine, nonhydroxylated forms.</p> <p>Tropoelastin with fibrillin scaffolding.</p> <p>Relaxed and stretched conformations.</p> <p><math>\alpha_1</math>-antitrypsin inhibits elastase.</p>	<p>Marfan's syndrome is caused by a defect in fibrillin.</p> <p>Emphysema can be caused by excess elastase activity.</p>
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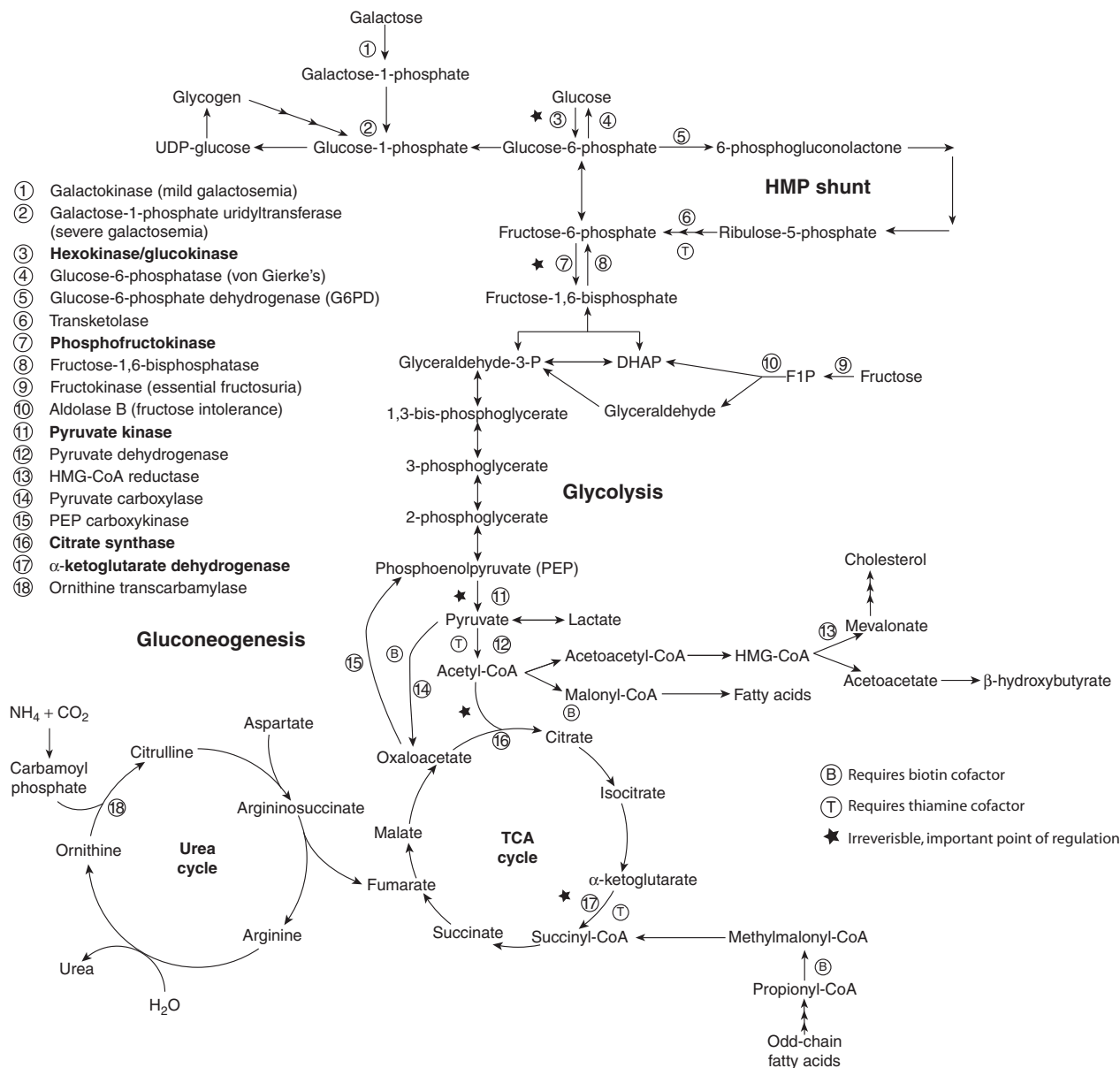
#### ► BIOCHEMISTRY—METABOLISM

#### Metabolism sites

Mitochondria	Fatty acid oxidation ( $\beta$ -oxidation), acetyl-CoA production, Krebs cycle.
Cytoplasm	Glycolysis, fatty acid synthesis, HMP shunt, protein synthesis (RER), steroid synthesis (SER).
Both	Gluconeogenesis, urea cycle, heme synthesis.

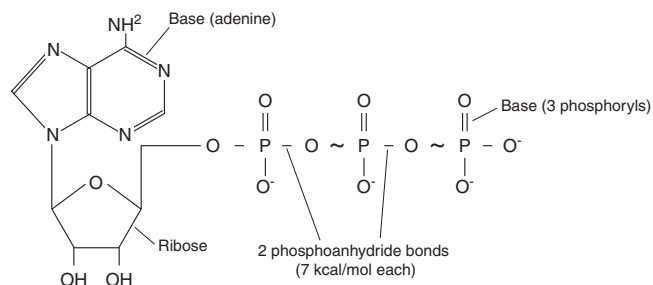
► BIOCHEMISTRY—METABOLISM (*continued*)

## Summary of pathways



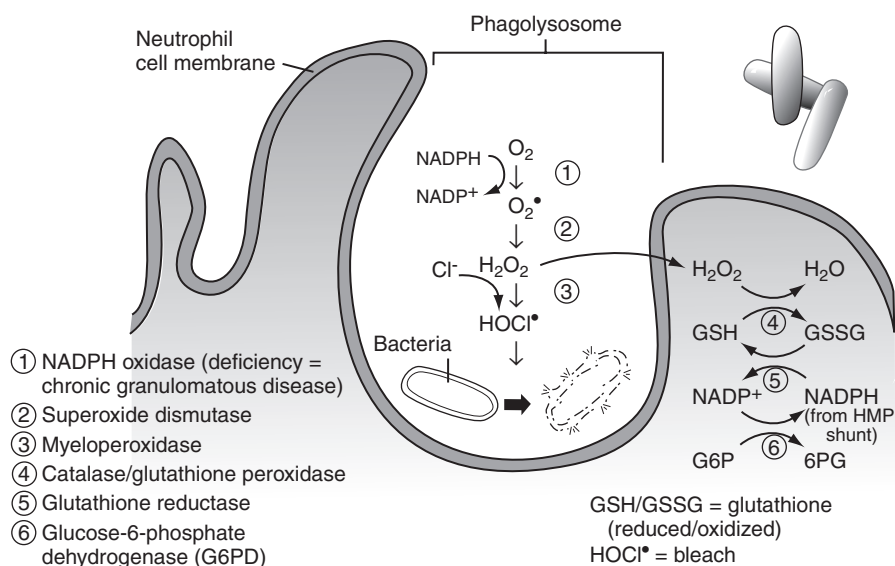
## ATP

Aerobic metabolism of glucose produces 38 ATP via malate shuttle, 36 ATP via G3P shuttle.  
 Anaerobic glycolysis produces only 2 net ATP per glucose molecule.  
 ATP hydrolysis can be coupled to energetically unfavorable reactions.



<b>Activated carriers</b>	Phosphoryl (ATP). Electrons (NADH, NADPH, FADH <sub>2</sub> ). Acyl (coenzyme A, lipoamide). CO <sub>2</sub> (biotin). 1-carbon units (tetrahydrofolates). CH <sub>3</sub> groups (SAM). Aldehydes (TPP).	
<b>S-adenosyl-methionine</b>	ATP + methionine → SAM. SAM transfers methyl units. Regeneration of methionine (and thus SAM) is dependent on vitamin B <sub>12</sub> .	SAM the methyl donor man.
<b>Universal electron acceptors</b>	Nicotinamides (NAD <sup>+</sup> , NADP <sup>+</sup> ) and flavin nucleotides (FAD <sup>+</sup> ). NAD <sup>+</sup> is generally used in <b>catabolic</b> processes to carry reducing equivalents away as NADH. NADPH is used in <b>anabolic</b> processes (steroid and fatty acid synthesis) as a supply of reducing equivalents.	NADPH is a product of the HMP shunt.  NADPH is used in: 1. Anabolic processes 2. Respiratory burst 3. P-450

### Oxygen-dependent respiratory burst



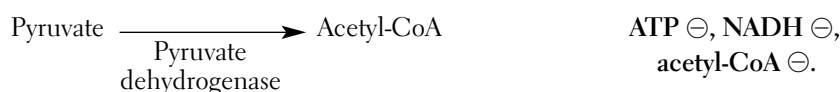
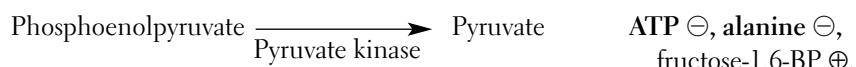
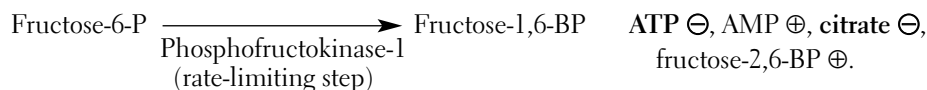
### Hexokinase vs. glucokinase

Hexokinase (ubiquitous)	High affinity, low capacity.
Glucokinase (liver)	Low affinity, high capacity.

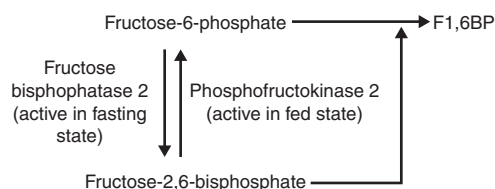
Feedback inhibited by glucose-6-phosphate.  
No feedback inhibition.  
Phosphorylates excess glucose (e.g., after a meal) to sequester it in the liver.

► BIOCHEMISTRY—METABOLISM (*continued*)**Glycolysis regulation, irreversible enzymes**

Net glycolysis (cytoplasm):



\* Glucokinase in liver; hexokinase in all other tissues.

**Regulation by F2,6BP**

**F2,6BP** is the most potent activator of phosphofructokinase (overrides inhibition by ATP and citrate).

**Glycolytic enzyme deficiency**Associated with **hemolytic anemia**.

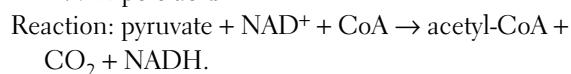
Pyruvate kinase (95%), glucose phosphate (4%), hexokinase, aldolase, triosephosphate isomerase, phosphate glycerate kinase, and enolase deficiencies.

RBCs metabolize glucose anaerobically (no mitochondria) and thus depend solely on glycolysis.

**Pyruvate dehydrogenase complex**

The complex contains 3 enzymes that require 5 cofactors (the first 4 B vitamins plus lipoic acid):

1. Pyrophosphate ( $B_1$ , thiamine; TPP)
2. FAD ( $B_2$ , riboflavin)
3. NAD ( $B_3$ , niacin)
4. CoA ( $B_5$ , pantothenate)
5. Lipoic acid



Activated by exercise:

- ↑  $\text{NAD}^+/\text{NADH}$  ratio
- ↑ ADP
- ↑  $\text{Ca}^{2+}$

The complex is similar to the  $\alpha$ -ketoglutarate dehydrogenase complex (same cofactors, similar substrate and action).

**Arsenic** inhibits lipoic acid:

- Vomiting
- Rice water stools
- Garlic breath

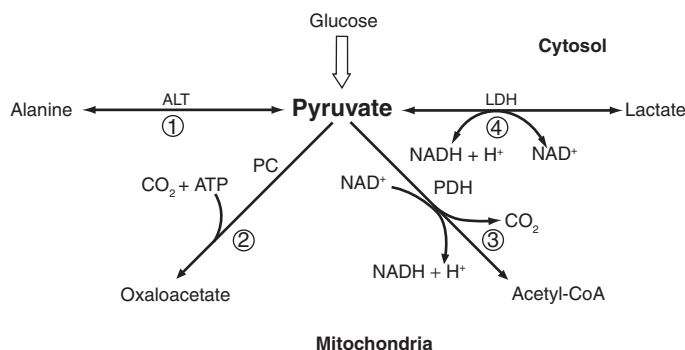
**Pyruvate dehydrogenase deficiency**

Causes backup of substrate (pyruvate and alanine), resulting in lactic acidosis. Can be congenital or acquired (as in alcoholics due to B<sub>1</sub> deficiency).

Findings: neurologic defects.

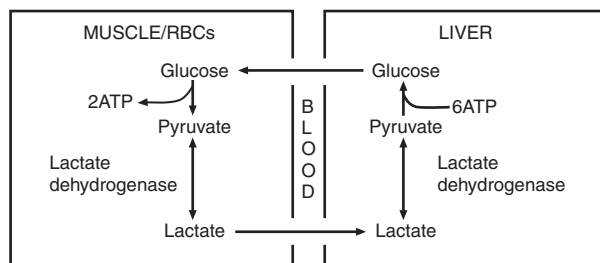
Treatment: ↑ intake of ketogenic nutrients (e.g., high fat content or ↑ lysine and leucine).

Lysine and Leucine—the only purely ketogenic amino acids.

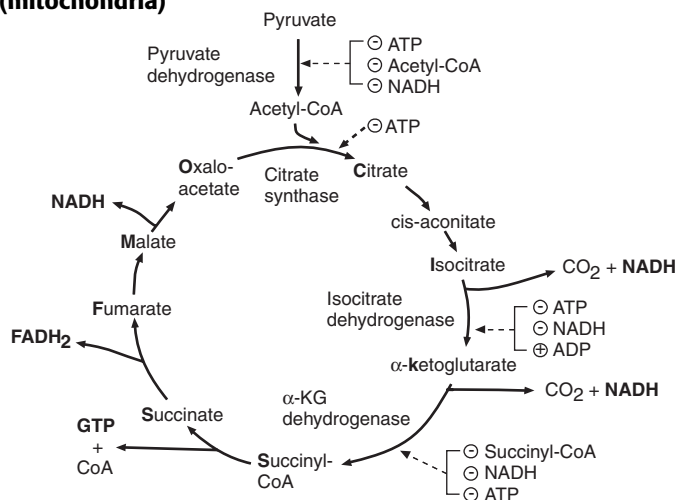
**Pyruvate metabolism**

6 ATP equivalents are needed to generate glucose from pyruvate.

1. Alanine carries amino groups to the liver from muscle.
2. Oxaloacetate can replenish TCA cycle or be used in gluconeogenesis.
3. Transition from glycolysis to the TCA cycle.
4. End of anaerobic glycolysis (major pathway in RBCs, leukocytes, kidney medulla, lens, testes, and cornea)

**Cori cycle**

Transfers excess reducing equivalents from RBCs and muscle to liver, allowing muscle to function anaerobically (net 2 ATP). Shifts metabolic burden to the liver.

**TCA cycle (mitochondria)**

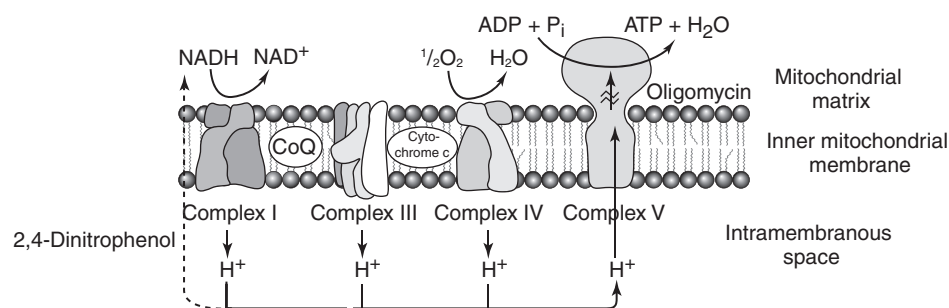
Produces 3 NADH, 1 FADH<sub>2</sub>, 2 CO<sub>2</sub>, 1 GTP per acetyl-CoA = 12 ATP/acetyl-CoA (2× everything per glucose)

α-ketoglutarate dehydrogenase complex requires same cofactors as the pyruvate dehydrogenase complex (B<sub>1</sub>, B<sub>2</sub>, B<sub>3</sub>, B<sub>5</sub>, lipoic acid).

Can I Keep Selling Sex For Money, Officer?

► **BIOCHEMISTRY—METABOLISM** (*continued*)

**Electron transport chain and oxidative phosphorylation**



Electron transport chain       $1 \text{ NADH} \rightarrow 3 \text{ ATP}; 1 \text{ FADH}_2 \rightarrow 2 \text{ ATP}.$

**Oxidative phosphorylation poisons**

Electron transport inhibitors	Directly inhibit electron transport, causing a $\downarrow$ proton gradient and block of ATP synthesis.	Rotenone, $\text{CN}^-$ , antimycin A, CO
ATPase inhibitors	Directly inhibit mitochondrial ATPase, causing an $\uparrow$ proton gradient, but no ATP is produced because electron transport stops.	Oligomycin
Uncoupling agents	$\downarrow$ permeability of membrane, causing a $\downarrow$ proton gradient and $\downarrow$ $\text{O}_2$ consumption. ATP synthesis stops, but electron transport continues.	UCP, 2,4-DNP, aspirin

**Gluconeogenesis, irreversible enzymes**

Pyruvate carboxylase	In mitochondria. Pyruvate $\rightarrow$ oxaloacetate.	Requires biotin, ATP. Activated by acetyl-CoA.
PEP carboxykinase	In cytosol. Oxaloacetate $\rightarrow$ phosphoenolpyruvate.	Requires GTP.
Fructose-1,6-bisphosphatase	In cytosol. Fructose-1,6-bisphosphate $\rightarrow$ fructose-6-P.	
Glucose-6-phosphatase	In ER. Glucose-6-P $\rightarrow$ glucose.	Pathway Produces Fresh Glucose.
Above enzymes found only in <b>liver, kidney, intestinal epithelium</b> . Muscle cannot participate in gluconeogenesis. Deficiency of the key gluconeogenic enzymes causes hypoglycemia.		

**Pentose phosphate pathway (HMP shunt)**

Produces NADPH, which is required for fatty acid and steroid biosynthesis and for glutathione reduction inside RBCs.

All reactions of this pathway occur in the cytoplasm. No ATP is used or produced.

Sites: lactating mammary glands, liver, adrenal cortex—all sites of fatty acid or steroid synthesis.

All reactions of this pathway occur in the cytoplasm. No ATP is used or produced.

Sites: lactating mammary glands, liver, adrenal cortex—all sites of fatty acid or steroid synthesis.

**Reactions**

Oxidative  
(irreversible)

**Key enzymes**

Glucose-6-phosphate dehydrogenase

**Products**

NADPH (for fatty acid and steroid synthesis, glutathione reduction, and cytochrome P-450)

Nonoxidative  
(reversible)

Transketolases (require thiamine)

Ribose-5-phosphate (for nucleotide synthesis), G3P, F6P (glycolytic intermediates)

**Glucose-6-phosphate dehydrogenase deficiency**

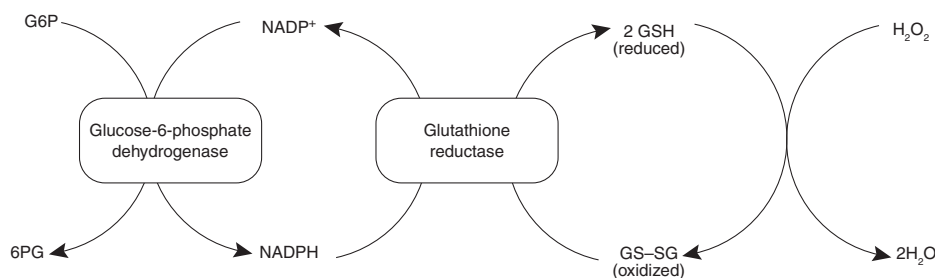
G6PD is a rate-limiting enzyme in HMP shunt (which yields NADPH). NADPH is necessary to keep glutathione reduced, which in turn detoxifies free radicals and peroxides. ↓ NADPH in RBCs leads to **hemolytic anemia** due to poor RBC defense against oxidizing agents (fava beans, sulfonamides, primaquine) and antituberculosis drugs.

G6PD deficiency is more prevalent among blacks.

**Heinz bodies**—altered Hemoglobin precipitates within RBCs.

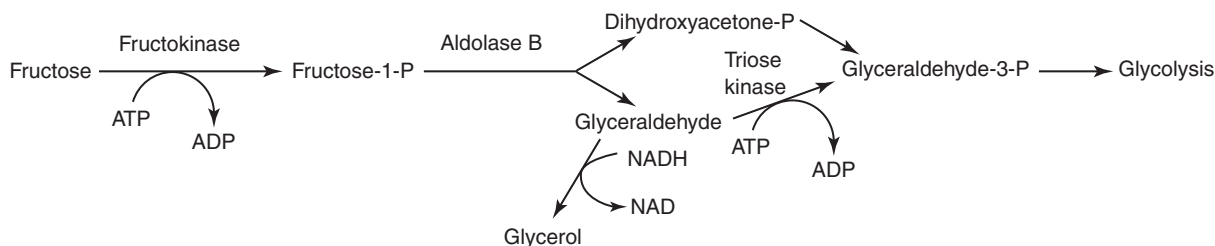
**X-linked recessive** disorder.

Increased malarial resistance.

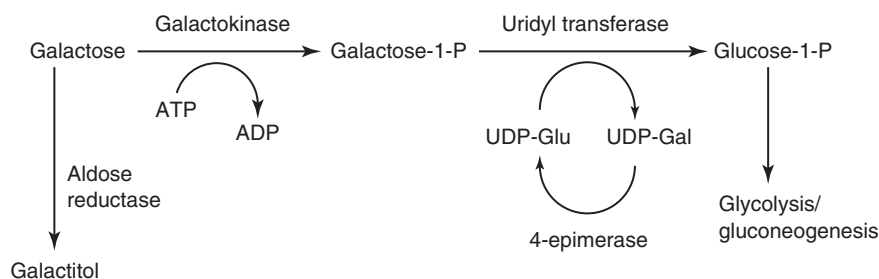


► BIOCHEMISTRY—METABOLISM (*continued*)**Disorders of fructose metabolism**

- Fructose intolerance** Hereditary deficiency of **aldolase B** (recessive). Fructose-1-phosphate accumulates, causing a ↓ in available phosphate, which results in inhibition of glycogenolysis and gluconeogenesis.  
Symptoms: hypoglycemia, jaundice, cirrhosis, vomiting.  
Treatment: must ↓ intake of both fructose and sucrose (glucose + fructose).
- Essential fructosuria** Involves a defect in **fructokinase** and is a benign, asymptomatic condition.  
Symptoms: fructose appears in blood and urine.

**FRUCTOSE METABOLISM (LIVER)****Disorders of galactose metabolism**

- Galactosemia** Absence of **galactose-1-phosphate uridylyltransferase**. Autosomal recessive. Damage is caused by accumulation of toxic substances (including galactitol) rather than absence of an essential compound.  
Symptoms: cataracts, hepatosplenomegaly, mental retardation.  
Treatment: exclude galactose and lactose (galactose + glucose) from diet.
- Galactokinase deficiency** Causes galactosemia and galactosuria, galactitol accumulation if galactose is present in diet.

**GALACTOSE METABOLISM****Lactase deficiency**

- Age-dependent and/or hereditary lactose intolerance (blacks, Asians) due to loss of brush border enzyme.  
Symptoms: bloating, cramps, osmotic diarrhea.  
Treatment: avoid milk or add lactase pills to diet.



**Amino acids**

## Essential

Ketogenic: Leu, Lys  
 Glucogenic/ketogenic: Ile, Phe, Trp  
 Glucogenic: Met, Thr, Val, Arg, His

All essential amino acids:

**PriVaTe TIM HALL.**

Arg and His are required during periods of growth.

## Acidic

Asp and Glu (negatively charged at body pH)

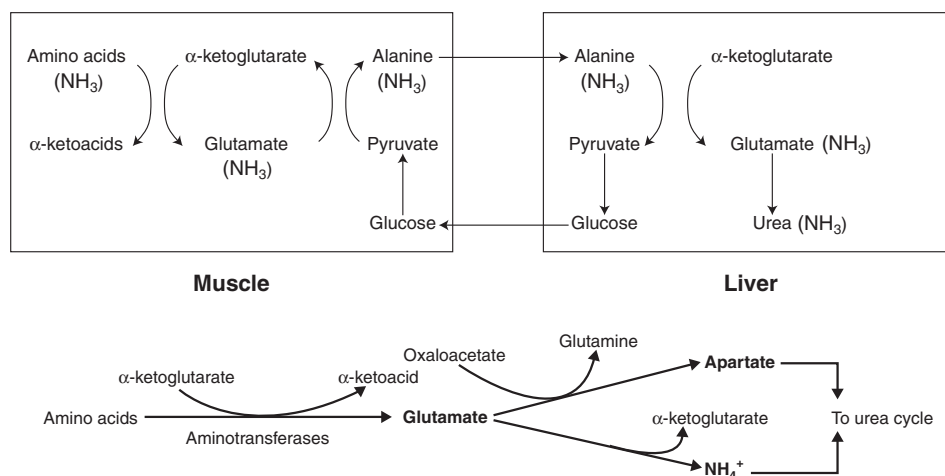
## Basic

Arg, Lys, and His.

Arg is most basic.

His has no charge at body pH.

Arg and Lys are ↑ in histones, which bind negatively charged DNA

**Transport of ammonium by alanine and glutamine**

## Hyperammonemia

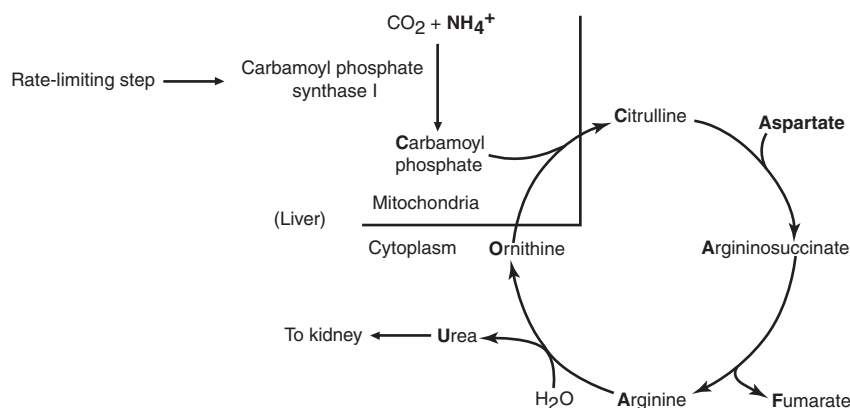
Can be acquired (e.g., liver disease) or hereditary (e.g., ornithine transcarbamoylase deficiency). Excess NH<sub>4</sub><sup>+</sup> depletes α-ketoglutarate, leading to inhibition of TCA cycle. Treatment: arginine.

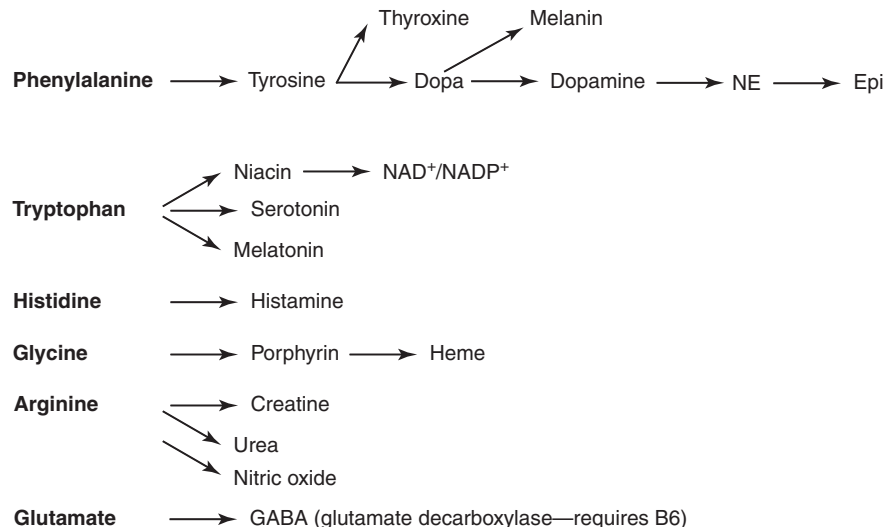
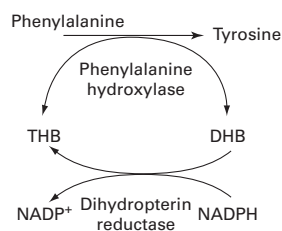
**Ammonia intoxication:** tremor, slurring of speech, somnolence, vomiting, cerebral edema, blurring of vision.

**Urea cycle**

Degrades amino acids into amino groups. Accounts for 90% of nitrogen in urine.

Ordinarily, Careless Crappers Are Also Frivolous About Urination.



► BIOCHEMISTRY—METABOLISM (*continued*)**Amino acid derivatives****Phenylketonuria**

Normally, phenylalanine is converted into tyrosine (nonessential aa). In PKU, there is ↓ phenylalanine hydroxylase or ↓ tetrahydrobiopterin cofactor. Tyrosine becomes essential and phenylalanine builds up, leading to excess phenylketones in urine. Findings: mental retardation, growth retardation, fair skin, eczema, musty body odor. Treatment: ↓ **phenylalanine** (contained in aspartame, e.g., NutraSweet) and ↑ **tyrosine** in diet.

Screened for at birth. Phenylketones—phenylacetate, phenyllactate, and phenylpyruvate. Autosomal-recessive disease. Incidence ≈ 1:10,000. Disorder of **aromatic** amino acid metabolism → musty body odor.

**Alkaptonuria (ochronosis)**

Congenital deficiency of **homogentisic acid oxidase** in the degradative pathway of tyrosine. Resulting alkapton bodies cause urine to turn black on standing. Also, the connective tissue is dark. Benign disease. May have debilitating arthralgias.

**Albinism**

Congenital deficiency of either of the following:

1. Tyrosinase (inability to synthesize melanin from tyrosine)—autosomal recessive
2. Defective tyrosine transporters (↓ amounts of tyrosine and thus melanin)

Can result from a lack of migration of neural crest cells.

Lack of melanin results in an ↑ risk of skin cancer. Variable inheritance due to locus heterogeneity.

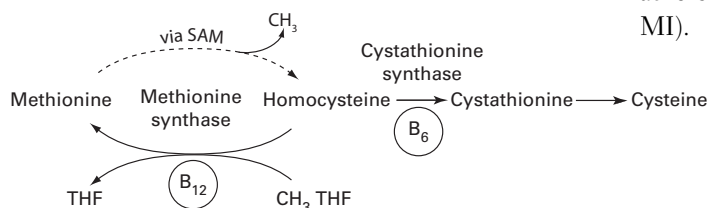
**Homocystinuria**

3 forms (all autosomal recessive):

1. Cystathionine synthase deficiency (treatment: ↓ Met and ↑ Cys in diet)
2. ↓ affinity of cystathionine synthase for pyridoxal phosphate (treatment: ↑↑ vitamin B<sub>6</sub> in diet)
3. Methionine synthase deficiency

Results in excess homocysteine in the urine. Cysteine becomes essential.

Can cause mental retardation, osteoporosis, tall stature, kyphosis, lens subluxation (downward and inward), and atherosclerosis (stroke and MI).

**Cystinuria**

Common (1:7000) inherited defect of renal tubular amino acid transporter for Cystine, Ornithine, Lysine, and Arginine in kidneys.

Excess cystine in urine can lead to the precipitation of **cystine kidney stones**.

**COLA.**

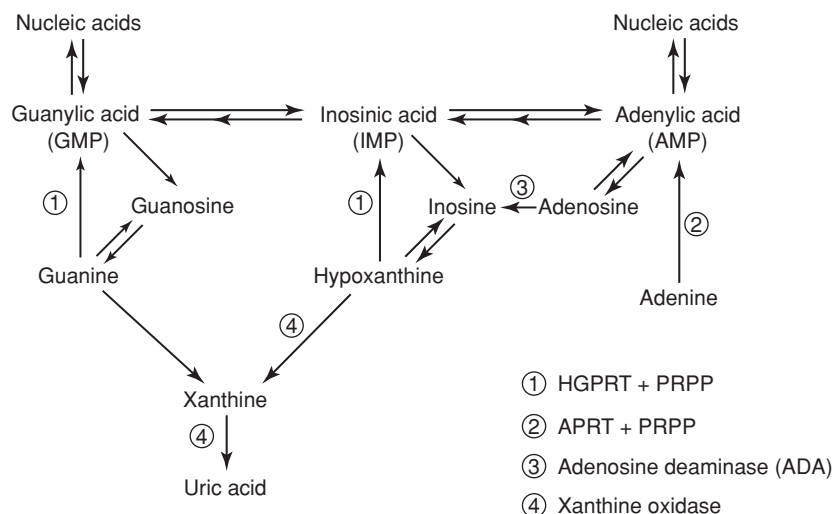
Treat with acetazolamide to alkalinize the urine.

**Maple syrup urine disease**

Blocked degradation of **branched** amino acids (Ile, Val, Leu) due to ↓ α-ketoacid dehydrogenase. Causes ↑ α-ketoacids in the blood, especially Leu. Causes severe CNS defects, mental retardation, and death.

Urine smells like maple syrup.

**I Love Vermont** maple syrup.

► BIOCHEMISTRY—METABOLISM (*continued*)**Purine salvage deficiencies**

Adenosine  
deaminase  
deficiency

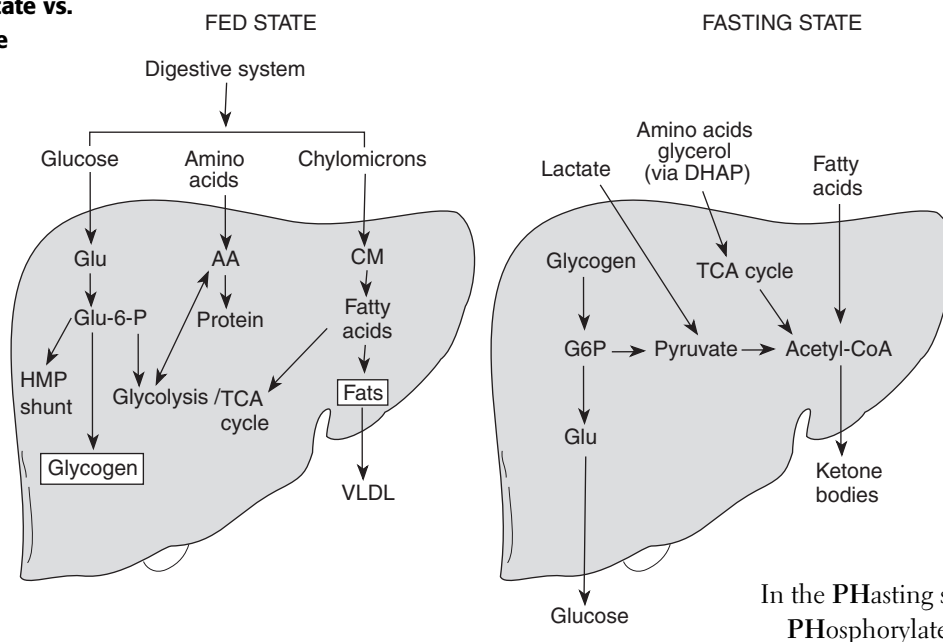
ADA deficiency can cause SCID. Excess ATP and dATP imbalances nucleotide pool via feedback inhibition of ribonucleotide reductase. This prevents DNA synthesis and thus ↓ lymphocyte count. 1st disease to be treated by experimental human gene therapy.

SCID—severe combined (T and B) immunodeficiency disease. **SCID** happens to **kids** (i.e., “bubble boy”).

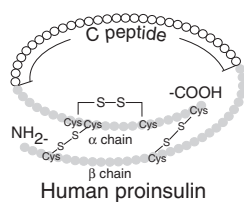
Lesch-Nyhan  
syndrome

Purine salvage problem owing to absence of HGPRTase, which converts hypoxanthine to inosine monophosphate (IMP) and guanine to guanosine monophosphate (GMP). X-linked recessive. Results in excess uric acid production. Findings: retardation, self-mutilation, aggression, hyperuricemia, gout, and choreoathetosis.

**LNS**—Lacks Nucleotide Salvage (purine).

**Liver: fed state vs. fasting state**

## Insulin



Made in  $\beta$  cells of pancreas. Required for adipose and skeletal muscle uptake of glucose.

GLUT2 receptors are found in  $\beta$  cells and GLUT4 in **muscle and fat**. Insulin inhibits glucagon release by  $\alpha$  cells of pancreas.

Serum C-peptide is not present with exogenous insulin intake.

Anabolic effects of insulin:

1.  $\uparrow$  glucose transport
2.  $\uparrow$  glycogen synthesis and storage
3.  $\uparrow$  triglyceride synthesis and storage
4.  $\uparrow$  Na retention (kidneys)
5.  $\uparrow$  protein synthesis (muscles)

Insulin moves glucose **Into** cells.

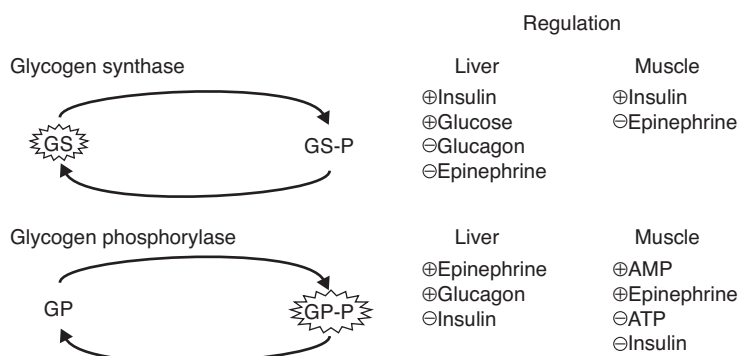
**BRICK L** (don't need insulin for glucose uptake):

Brain  
RBCs  
Intestine  
Cornea  
Kidney  
Liver

GLUT1: RBCs, brain

GLUT2 (bidirectional):  $\beta$  islet cells, liver, kidney

GLUT4 (insulin responsive): adipose tissue, skeletal muscle

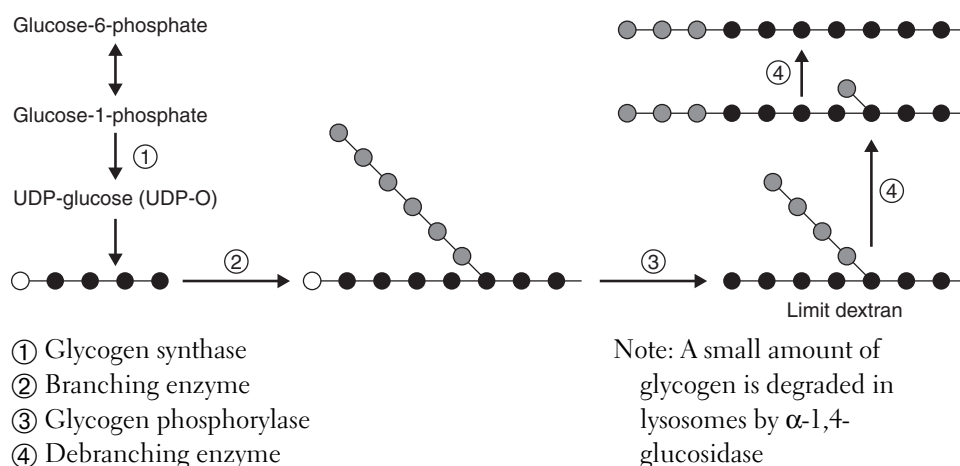


## Glycogen

Skeletal muscle  
Hepatocytes

Rapidly metabolizes glucose from glycogen during exercise.

Storage depot to maintain blood sugar at appropriate levels.



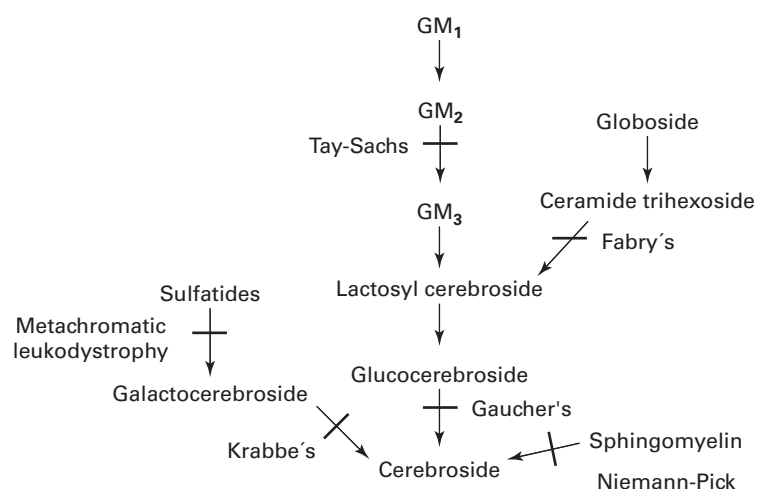
► BIOCHEMISTRY—METABOLISM (*continued*)

<b>Glycogen storage diseases</b>	12 types, all resulting in abnormal glycogen metabolism and an accumulation of glycogen within cells.		Very Poor Carbohydrate Metabolism.
<b>Disease</b>	<b>Findings</b>	<b>Deficient enzyme</b>	<b>Comments</b>
Von Gierke's disease (Type I)	Severe fasting hypoglycemia, ↑↑ glycogen in liver, ↑ blood lactate, hepatomegaly.	Glucose-6-phosphate.	The liver becomes a muscle. (Think about it.)
Pompe's disease (Type II)	Cardiomegaly and systemic findings leading to early death.	Lysosomal $\alpha$ -1,4-glucosidase (acid maltase).	Pompe's trashes the Pump (heart, liver, and muscle).
Cori's disease (Type III)	Milder form of Type I with normal blood lactate levels.	Debranching enzyme $\alpha$ -1,6-glucosidase.	
McArdle's disease (Type V)	↑glycogen in muscle, but cannot break it down, leading to painful muscle cramps, myoglobinuria with strenuous exercise.	Skeletal muscle glycogen phosphorylase.	McArdle's = Muscle.

**Lysosomal storage diseases**

Each is caused by a deficiency in one of the many lysosomal enzymes.

Disease	Findings	Deficient enzyme	Accumulated substrate	Inheritance
<b>Sphingoliposes</b>				
Fabry's disease	Peripheral neuropathy of hands/feet, angiokeratomas, cardiovascular/renal disease	$\alpha$ -galactosidase A	Ceramide trihexoside	XR
Gaucher's disease (most common)	Hepatosplenomegaly, aseptic necrosis of femur, bone crises, Gaucher's cells (macrophages)	$\beta$ -glucocerebrosidase	Glucocerebroside	AR
Niemann-Pick disease	Progressive neurodegeneration, hepatosplenomegaly, cherry-red spot (on macula)	Sphingomyelinase	Sphingomyelin	AR
Tay-Sachs disease	Progressive neurodegeneration, developmental delay, cherry-red spot, lysosomes with onion skin	Hexosaminidase A	GM <sub>2</sub> ganglioside	AR
Krabbe's disease	Peripheral neuropathy, developmental delay, optic atrophy	$\beta$ -galactosidase	Galactocerebroside	AR
Metachromatic leukodystrophy	Central and peripheral demyelination with ataxia, dementia	Arylsulfatase A	Cerebroside sulfate	AR
<b>Mucopolysaccharidoses</b>				
Hurler's syndrome	Developmental delay, gargoylism, airway obstruction, corneal clouding, hepatosplenomegaly	$\alpha$ -L-iduronidase	Heparan sulfate, dermatan sulfate	AR
Hunter's syndrome	Mild Hurler's + aggressive behavior, no corneal clouding	Iduronate sulfatase	Heparan sulfate, dermatan sulfate	XR

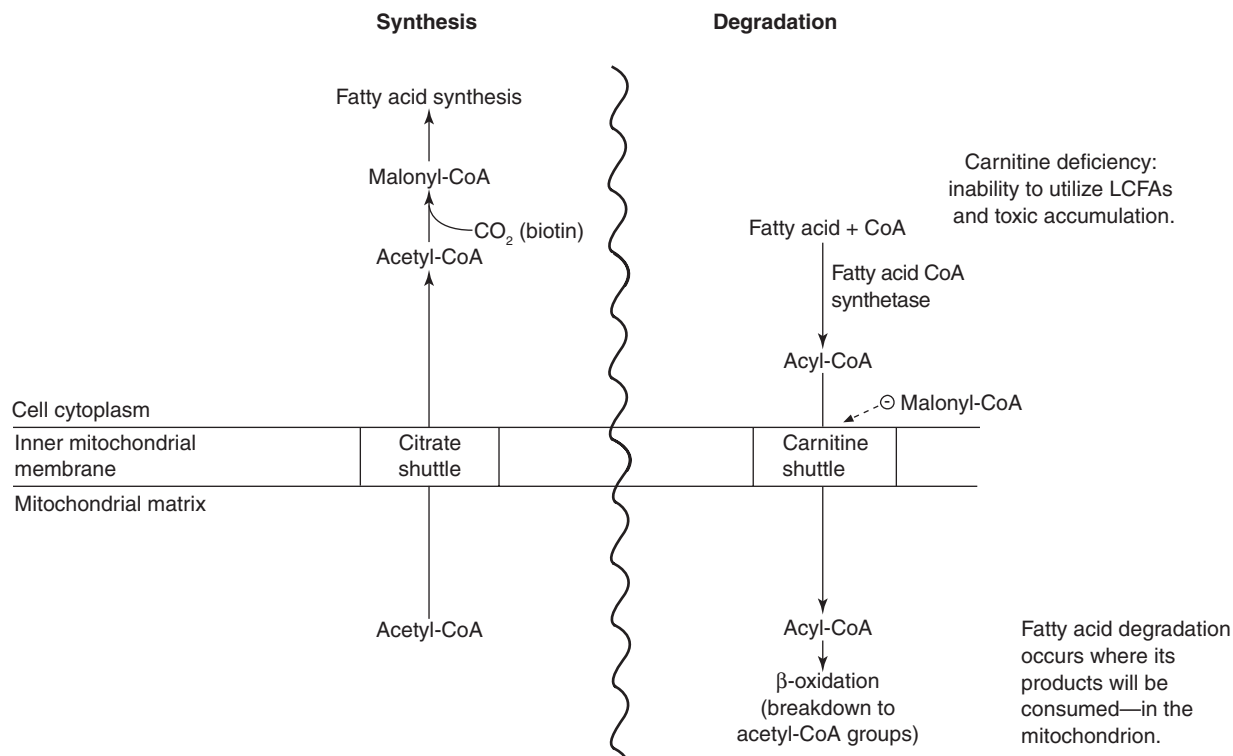


**No man picks (Niemann-Pick)**  
his nose with his **sphinger**  
(**sphingomyelinase**).

**Tay-SaX (Tay-Sachs)**  
lacks heXosaminidase.

**Hunters** aim for the **X**  
(**X**-linked recessive).

Increased incidence of Tay-Sachs,  
Niemann-Pick, and some forms  
of Gaucher's disease in  
Ashkenazi Jews.

► BIOCHEMISTRY—METABOLISM (*continued*)**Fatty acid metabolism sites****Ketone bodies**

In liver: fatty acid and amino acids  $\rightarrow$  **acetoacetate** +  **$\beta$ -hydroxybutyrate** (to be used in muscle and brain). Ketone bodies found in prolonged starvation and diabetic ketoacidosis. Excreted in urine. Made from HMG-CoA. Ketone bodies are metabolized by the brain to 2 molecules of acetyl-CoA.

Breath smells like acetone (fruity odor).  
Urine test for ketones does not detect  $\beta$ -hydroxybutyrate (favored by high redox state).

**Cholesterol synthesis**

Rate-limiting step is catalyzed by **HMG-CoA reductase**, which converts HMG-CoA to mevalonate.  $\frac{2}{3}$  of plasma cholesterol is esterified by lecithin-cholesterol acyltransferase (LCAT).

**Lovastatin** inhibits HMG-CoA reductase.

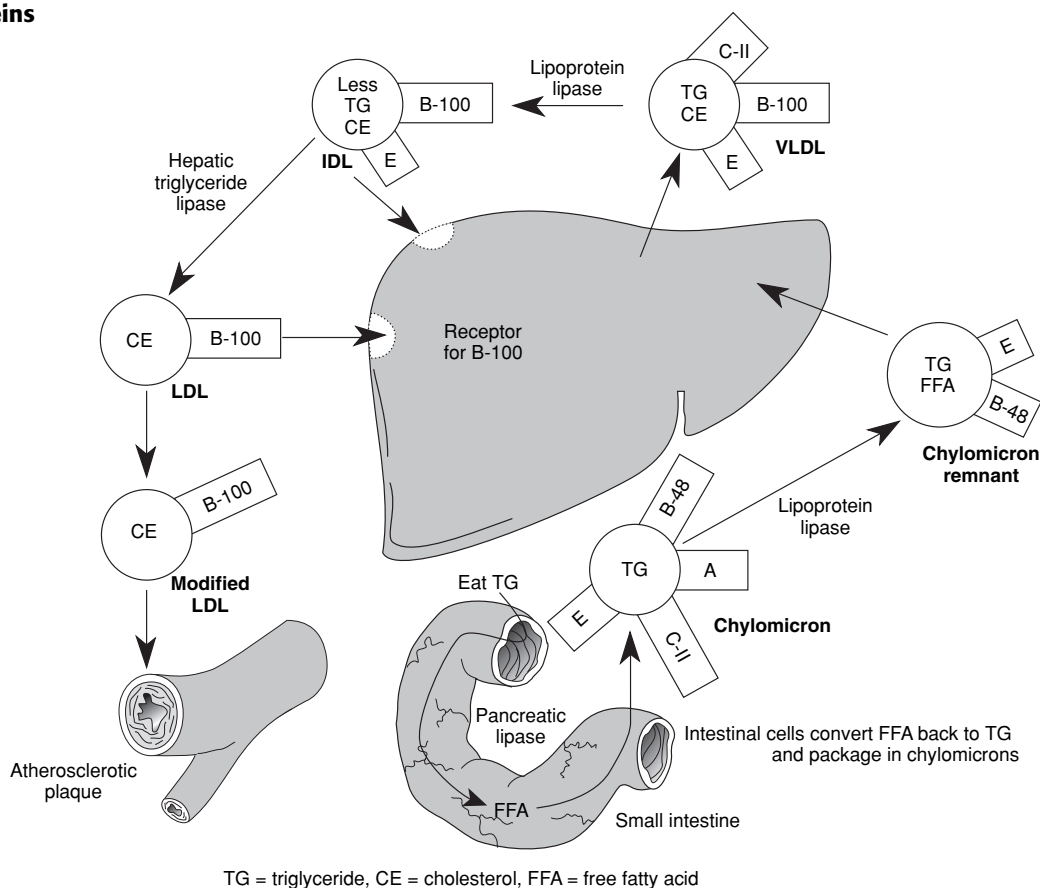
**Essential fatty acids**

Linoleic and linolenic acids.  
Arachidonic acid, if linoleic acid is absent.

Eicosanoids are dependent on essential fatty acids.



## Lipoproteins



Pancreatic lipase—degradation of dietary TG in small intestine.

Lipoprotein lipase—degradation of TG circulating in chylomicrons and VLDLs.

Hepatic TG lipase—degradation of TG remaining in IDL.

Hormone-sensitive lipase—degradation of TG stored in adipocytes.

Lecithin-cholesterol acyltransferase (LCAT)—catalyzes esterification of cholesterol.

Cholesterol ester transfer protein (CETP)—mediates transfer of cholesterol esters to other lipoprotein particles.

### Major apolipoproteins

A-I—Activates LCAT.

B-100—Binds to LDL receptor, mediates VLDL secretion.

C-II—Cofactor for lipoprotein lipase.

B-48—Mediates chylomicron secretion.

E—Mediates Extra (remnant) uptake.

► BIOCHEMISTRY—METABOLISM (*continued*)

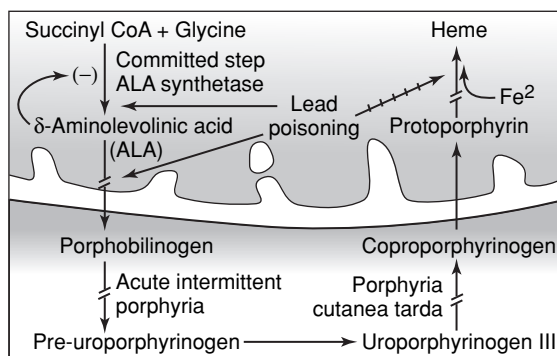
<b>Lipoprotein functions</b>	Lipoproteins are composed of varying proportions of cholesterol, triglycerides, and phospholipids. LDL and HDL carry most cholesterol. LDL transports cholesterol from liver to tissue; HDL transports it from periphery to liver.		HDL is <b>Healthy</b> . LDL is <b>Lousy</b> .
Chylomicron	<b>Function and route</b> Delivers dietary triglycerides to peripheral tissues and dietary cholesterol to liver. Secreted by intestinal epithelial cells. Excess causes pancreatitis, lipemia retinalis, and eruptive xanthomas.	<b>Apolipoproteins</b> B-48, A, C, and E	
VLDL	Delivers hepatic triglycerides to peripheral tissues. Secreted by liver. Excess causes pancreatitis.	B-100, C-II, and E	
IDL	Formed in the degradation of VLDL. Delivers triglycerides and cholesterol to liver, where they are degraded to LDL.	B-100 and E	
LDL	Delivers hepatic cholesterol to peripheral tissues. Formed by lipoprotein lipase modification of VLDL in the peripheral tissue. Taken up by target cells via receptor-mediated endocytosis. Excess causes atherosclerosis, xanthomas, and arcus corneae.	B-100	
HDL	Mediates centripetal transport of cholesterol (reverse cholesterol transport, from periphery to liver). Acts as a repository for apoC and apoE (which are needed for chylomicron and VLDL metabolism). Secreted from both liver and intestine.		

**Familial dyslipidemias**

Type	Increased	Elevated blood levels	Pathophysiology
I—hyperchylomicronemia	Chylomicrons	TG, cholesterol	Lipoprotein lipase deficiency or altered apolipoprotein C-II
IIa—hypercholesterolemia	LDL	Cholesterol	↓ LDL receptors
IIb—combined hyperlipidemia	LDL, VLDL	TG, cholesterol	Hepatic overproduction of VLDL
III—dysbetalipoproteinemia	IDL, VLDL	TG, cholesterol	Altered apolipoprotein E
IV—hypertriglyceridemia	VLDL	TG	Hepatic overproduction of VLDL
V—mixed hypertriglyceridemia	VLDL, chylomicrons	TG, cholesterol	↑ production/↓ clearance of VLDL and chylomicrons

**Heme synthesis**

Underproduction of heme causes microcytic hypochromic anemia. Accumulation of intermediates causes porphyrias.

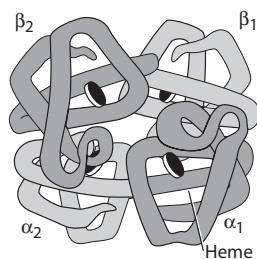
**Porphyrias**

	Affected enzyme	Accumulated substrate in urine	
Lead poisoning	Ferrochelatase and ALA dehydratase	Coproporphyrin and ALA	
Acute intermittent porphyria	Uroporphyrinogen I synthase	Porphobilinogen and $\delta$ -ALA	Symptoms = 5 P's: Painful abdomen, Pink urine Polyneuropathy Psychological disturbances Precipitated by drugs
Porphyria cutanea tarda	Uroporphyrinogen decarboxylase	Uroporphyrin (tea-colored)	

**Heme catabolism**

Heme is scavenged from RBCs and  $\text{Fe}^{2+}$  is reused. Heme  $\rightarrow$  biliverdin  $\rightarrow$  bilirubin (sparingly water soluble, toxic to CNS, transported by albumin). Bilirubin is removed from blood by liver, conjugated with glucuronate, and excreted in bile. Some urobilinogen, an intestinal intermediate, is reabsorbed into blood and excreted as urobilin into urine.

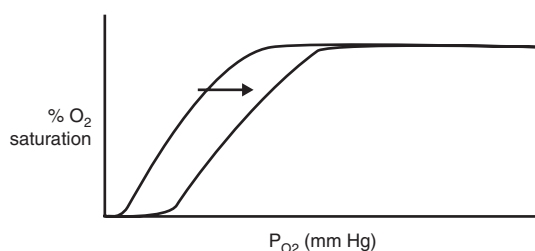
## ► BIOCHEMISTRY—METABOLISM (continued)

**Hemoglobin**

Hemoglobin is composed of 4 polypeptide subunits (2  $\alpha$  and 2  $\beta$ ) and exists in 2 forms:

1. T (taut) form has low affinity for  $O_2$ .
2. R (relaxed) form has high affinity for  $O_2$  (300 $\times$ ). Hemoglobin exhibits positive cooperativity and negative allostery (accounts for the sigmoid-shaped  $O_2$  dissociation curve for hemoglobin), unlike myoglobin.

↑  $Cl^-$ ,  $H^+$ ,  $CO_2$ , 2,3-BPG, and temperature favor T form over R form (shifts dissociation curve to right, leading to ↑  $O_2$  unloading).



When you're **Relaxed**, you do your job better (carry  $O_2$ ). Fetal hemoglobin (2 $\alpha$  and 2 $\gamma$  subunits) has lower affinity for 2,3-BPG than adult hemoglobin (HbA) and thus has higher affinity for  $O_2$ .

Fetal hemoglobin (2 $\alpha$  and 2 $\gamma$  subunits) has lower affinity for 2,3-BPG than adult hemoglobin (HbA) and thus has higher affinity for  $O_2$ .

**CO<sub>2</sub> transport in blood**

$CO_2$  (primarily as bicarbonate) binds to amino acids in globin chain at N terminus, but not to heme.

$CO_2$  binding favors T (taut) form of hemoglobin promoting  $O_2$  unloading (negative allosteric regulation).

$CO_2$  must be transported from tissue to lungs, the reverse of  $O_2$ .

**Hemoglobin modifications****Methemoglobin**

Oxidized form of hemoglobin (ferric,  $Fe^{3+}$ ) that does not bind  $O_2$  as readily, but has ↑ affinity for  $CN^-$ .

Iron in hemoglobin is normally in a reduced state (ferrous,  $Fe^{2+}$ ).

Treat toxic levels of **METH**emoglobin with **METH**ylene blue.

Administer nitrates in cyanide poisoning to oxidize hemoglobin to methemoglobin.

**Carboxyhemoglobin**

Form of hemoglobin bound to CO in place of  $O_2$ .

CO has a 200 $\times$  greater affinity than  $O_2$  for hemoglobin.

**Polymerase chain reaction (PCR)**

Molecular biology laboratory procedure that is used to synthesize many copies of a desired fragment of DNA.

Steps:

1. DNA is denatured by heating to generate 2 separate strands
2. During cooling, excess premade DNA primers anneal to a specific sequence on each strand to be amplified
3. Heat-stable DNA polymerase replicates the DNA sequence following each primer

These steps are repeated multiple times for DNA sequence amplification.

**Molecular biology techniques**

Southern blot

A DNA sample is electrophoresed on a gel and then transferred to a filter. The filter is then soaked in a denaturant and subsequently exposed to a labeled DNA probe that recognizes and anneals to its complementary strand. The resulting double-stranded labeled piece of DNA is visualized when the filter is exposed to film.

**SNoW DRoP:**

Southern = DNA

Northern = RNA

Western = Protein

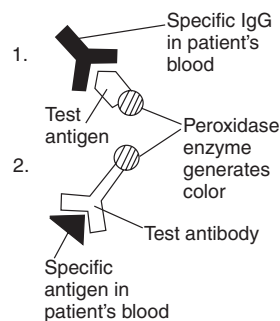
Northern blot

Similar technique, except that Northern blotting involves radioactive DNA probe binding to sample **RNA**.

Western blot

Sample protein is separated via gel electrophoresis and transferred to a filter. Labeled antibody is used to bind to relevant **protein**.

**Enzyme-linked immunosorbent assay (ELISA)**



A rapid immunologic technique testing for **antigen-antibody** reactivity.

Patient's blood sample is probed with either

1. Test antigen (coupled to color-generating enzyme)—to see if immune system recognizes it; or
2. Test antibody (coupled to color-generating enzyme)—to see if a certain antigen is present

If the target substance is present in the sample, the test solution will have an intense color reaction, indicating a positive test result.

ELISA is used in many laboratories to determine whether a particular antibody (e.g., anti-HIV) is present in a patient's blood sample. Both the sensitivity and the specificity of ELISA approach 100%, but both false positive and false negative results do occur.

**Fluorescence in situ hybridization (FISH)**

Fluorescent probe binds to specific gene site of interest.

Specific localization of genes and direct visualization of anomalies at molecular level.

## ► BIOCHEMISTRY—GENETICS

**Genetic terms**

Codominance	Neither of two alleles is dominant (e.g., blood groups).
Variable expression	Nature and severity of the phenotype varies from 1 individual to another.
Incomplete penetrance	Not all individuals with a mutant genotype show the mutant phenotype.
Pleiotropy	1 gene has > 1 effect on an individual's phenotype.
Imprinting	Differences in phenotype depend on whether the mutation is of maternal or paternal origin (e.g., AngelMan's syndrome [Maternal], Prader-Willi syndrome [Paternal]).
Anticipation	Severity of disease worsens or age of onset of disease is earlier in succeeding generations (e.g., Huntington's disease).
Loss of heterozygosity	If a patient inherits or develops a mutation in a tumor suppressor gene, the complementary allele must be deleted/mutated before cancer develops. This is not true of oncogenes.
Dominant negative mutation	Exerts a <b>dominant effect</b> . A heterozygote produces a nonfunctional altered protein that also prevents the normal gene product from functioning.
Linkage disequilibrium	Tendency for certain alleles at 2 linked loci to occur together more often than expected by chance. Measured in a population, not in a family, and often varies in different populations.
Mosaicism	Occurs when cells in the body have different genetic makeup (e.g., lyonization—random X inactivation in females).
Locus heterogeneity	Mutations at different loci can produce the same phenotype (e.g., albinism).

**Hardy-Weinberg population genetics**

If a population is in Hardy-Weinberg equilibrium, then:  
 Disease prevalence:  $p^2 + 2pq + q^2 = 1$   
 Allele prevalence:  $p + q = 1$   
 $p$  and  $q$  are separate alleles;  $2pq$  = heterozygote prevalence.

Hardy-Weinberg law assumes:

1. There is no mutation occurring at the locus
2. There is no selection for any of the genotypes at the locus
3. Mating is completely random
4. There is no migration into or out of the population being considered

**Imprinting**

At a single locus, only one allele is active; the other is inactive (imprinted/inactivated by methylation).

Deletion of the active allele → disease.

Prader-Willi      Deletion of normally active paternal allele.

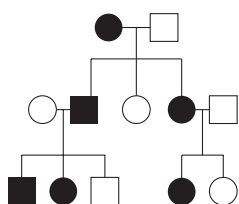
Mental retardation, obesity, hypogonadism, hypotonia.

Angelman's syndrome      Deletion of normally active maternal allele.

Mental retardation, seizures, ataxia, inappropriate laughter (happy puppet).

## Modes of inheritance

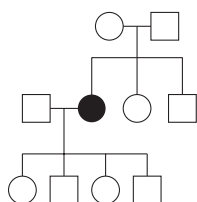
### Autosomal dominant



Often due to defects in structural genes. Many generations, both male and female, affected.

Often pleiotropic and, in many cases, present clinically after puberty. Family history crucial to diagnosis.

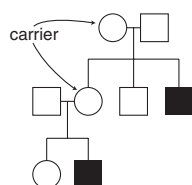
### Autosomal recessive



25% of offspring from 2 carrier parents are affected. Often due to enzyme deficiencies. Usually seen in only 1 generation.

Commonly more severe than dominant disorders; patients often present in childhood.

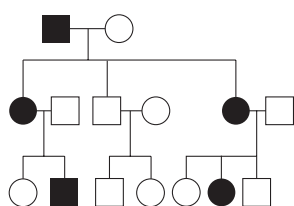
### X-linked recessive



Sons of heterozygous mothers have a 50% chance of being affected. No male-to-male transmission.

Commonly more severe in males. Heterozygous females may be affected.

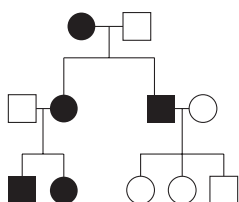
### X-linked dominant



Transmitted through both parents. Either male or female offspring of the affected mother may be affected, while **all** female offspring of the affected father are diseased.

Hypophosphatemic rickets.

### Mitochondrial inheritance



Transmitted only through mother. All offspring of affected females may show signs of disease.

Leber's hereditary optic neuropathy; mitochondrial myopathies.

► BIOCHEMISTRY—GENETICS (*continued*)**Autosomal-dominant diseases**

Adult polycystic kidney disease	<b>Always bilateral</b> , massive enlargement of kidneys due to multiple large cysts. Patients present with pain, hematuria, hypertension, progressive renal failure. 90% of cases are due to mutation in <i>APKD1</i> (chromosome 16). Associated with polycystic liver disease, <b>berry aneurysms</b> , mitral valve prolapse. Juvenile form is recessive.
Familial hypercholesterolemia (hyperlipidemia type IIA)	Elevated LDL owing to defective or absent LDL receptor. Heterozygotes (1:500) have cholesterol $\approx$ 300 mg/dL. Homozygotes (very rare) have cholesterol $\approx$ 700+ mg/dL, severe atherosclerotic disease early in life, and tendon xanthomas (classically in the Achilles tendon); MI may develop before age 20.
Marfan's syndrome	Fibrillin gene mutation $\rightarrow$ connective tissue disorders. Skeletal abnormalities—tall with long extremities (arachnodactyly), pectus excavatum, hyperextensive joints, and long, tapering fingers and toes (see Image 109). Cardiovascular—cystic medial necrosis of aorta $\rightarrow$ aortic incompetence and dissecting aortic aneurysms. Floppy mitral valve. Ocular—subluxation of lenses.
Neurofibromatosis type 1 (von Recklinghausen's disease)	Findings: café-au-lait spots, neural tumors, Lisch nodules (pigmented iris hamartomas). Also marked by skeletal disorders (e.g., scoliosis), optic pathway gliomas, pheochromocytoma, and $\uparrow$ tumor susceptibility. On long arm of chromosome 17; 17 letters in von Recklinghausen.
Neurofibromatosis type 2	Bilateral acoustic neuroma, juvenile cataracts. <i>NF2</i> gene on chromosome 22; type 2 = 22.
Tuberous sclerosis	Findings: facial lesions (adenoma sebaceum), hypopigmented “ash leaf spots” on skin, cortical and retinal hamartomas, seizures, mental retardation, renal cysts, cardiac rhabdomyomas. Incomplete penetrance, variable presentation.
Von Hippel–Lindau disease	Findings: hemangioblastomas of retina/cerebellum/medulla; about half of affected individuals develop multiple bilateral renal cell carcinomas and other tumors. Associated with deletion of <i>VHL</i> gene (tumor suppressor) on chromosome 3 (3p). Von Hippel–Lindau = 3 words for chromosome 3.
Huntington's disease	Findings: depression, progressive dementia, choreiform movements, caudate atrophy, and $\downarrow$ levels of GABA and ACh in the brain. Symptoms manifest in affected individuals between the ages of 20 and 50. Gene located on chromosome 4; triplet repeat disorder. “Hunting 4 food.”
Familial adenomatous polyposis	Colon becomes covered with adenomatous polyps after puberty. Progresses to colon cancer unless resected. Deletion on chromosome 5; 5 letters in “polyp.”
Hereditary spherocytosis	Spheroid erythrocytes; hemolytic anemia; increased MCHC. Splenectomy is curative.
Achondroplasia	Autosomal-dominant cell-signaling defect of fibroblast growth factor (FGF) receptor 3. Results in dwarfism; short limbs, but head and trunk are normal size. Associated with advanced paternal age.

**Autosomal-recessive diseases**

Cystic fibrosis, albinism,  $\alpha_1$ -antitrypsin deficiency, phenylketonuria, thalassemias, sickle cell anemias, glycogen storage diseases, mucopolysaccharidoses (except Hunter's), sphingolipidoses (except Fabry's), infant polycystic kidney disease, hemochromatosis.



<b>Cystic fibrosis</b>	Autosomal-recessive defect in <i>CFTR</i> gene on chromosome 7, commonly deletion of Phe 508. <i>CFTR</i> channel secretes $\text{Cl}^-$ in lungs and GI tract and reabsorbs $\text{Cl}^-$ from sweat. Defective $\text{Cl}^-$ channel $\rightarrow$ secretion of abnormally thick mucus that plugs lungs, pancreas, and liver $\rightarrow$ recurrent pulmonary infections ( <i>Pseudomonas</i> species and <i>S. aureus</i> ), chronic bronchitis, bronchiectasis, pancreatic insufficiency (malabsorption and steatorrhea), meconium ileus in newborns. $\uparrow$ concentration of $\text{Cl}^-$ ions in sweat test is diagnostic.	Infertility in males due to absent vas deferens. Fat-soluble vitamin deficiencies (A, D, E, K). Can present as failure to thrive in infancy. Most common lethal genetic disease of Caucasians. Treatment: N-acetylcysteine to loosen mucous plugs.
<b>X-linked recessive disorders</b>	Bruton's agammaglobulinemia, Wiskott-Aldrich syndrome, Fragile X, G6PD deficiency, Ocular albinism, Lesch-Nyhan syndrome, Duchenne's muscular dystrophy, Hemophilia A and B, Fabry's disease, Hunter's syndrome. Female carriers of X-linked recessive disorders are rarely affected because of random inactivation of X chromosomes in each cell.	Be Wise, Fool's <b>GOLD</b> Heeds False Hope.
<b>Muscular dystrophies</b>		
Duchenne's (X-linked)	Frame-shift mutation $\rightarrow$ deletion of dystrophin gene $\rightarrow$ accelerated muscle breakdown. Onset before 5 years of age. Weakness begins in pelvic girdle muscles and progresses superiorly. Pseudohypertrophy of calf muscles due to fibrofatty replacement of muscle; cardiac myopathy. The use of Gowers' maneuver, requiring assistance of the upper extremities to stand up, is characteristic (indicates proximal lower limb weakness).	Duchenne's = Deleted Dystrophin. Diagnose muscular dystrophies by $\uparrow$ CPK and muscle biopsy.
Becker's	Mutated dystrophin gene is less severe than Duchenne's.	
<b>Fragile X syndrome</b>	X-linked defect affecting the methylation and expression of the <i>FMRI</i> gene. The 2nd most common cause of genetic mental retardation (the most common cause is Down syndrome). Associated with macro-orchidism (enlarged testes), long face with a large jaw, large everted ears, and autism.	Triplet repeat disorder $(\text{CGG})_n$ that may show genetic anticipation (germlike expansion in females). Fragile <b>X</b> = eXtra-large testes, jaw, ears.
<b>Trinucleotide repeat expansion diseases</b>	Huntington's disease, myotonic dystrophy, Friedreich's ataxia, fragile <b>X</b> syndrome. May show anticipation (disease severity $\uparrow$ and age of onset $\downarrow$ in successive generations).	<b>Try</b> (trinucleotide) <b>hunting</b> for my fried eggs ( <b>X</b> ).

► BIOCHEMISTRY–GENETICS (*continued*)**Autosomal trisomies**

Down syndrome  
(trisomy 21), 1:700

Most common chromosomal disorder and cause of congenital mental retardation. Findings: mental retardation, flat facial profile, prominent epicanthal folds, simian crease, duodenal atresia, congenital heart disease (most common malformation is septum primum–type ASD due to endocardial cushion defects), Alzheimer's disease in affected individuals > 35 years old, ↑ risk of ALL.

Drinking age (21).  
↓ levels of  $\alpha$ -fetoprotein,  
↑  $\beta$ -hCG, ↑ nuchal  
translucency.

95% of cases due to meiotic nondisjunction of homologous chromosomes; associated with advanced maternal age (from 1:1500 in women < 20 to 1:25 in women > 45). 4% of cases due to Robertsonian translocation, and 1% of cases due to Down mosaicism (no maternal association) (see Image 110).

Edwards' syndrome  
(trisomy 18),  
1:8000

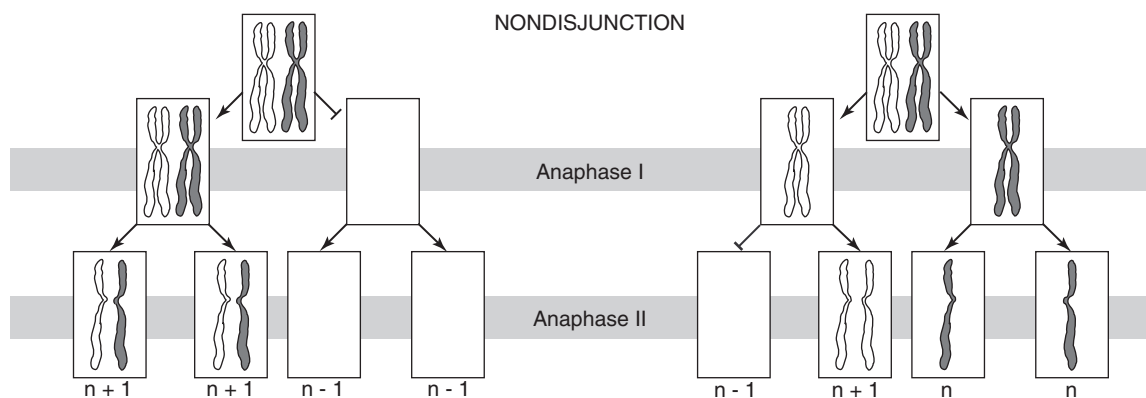
Findings: severe mental retardation, rocker bottom feet, low-set ears, micrognathia (small jaw), congenital heart disease, clenched hands, prominent occiput. Death usually occurs within 1 year of birth.

Election age (18).

Patau's syndrome  
(trisomy 13),  
1:15,000

Findings: severe mental retardation, microphthalmia, microcephaly, cleft lip/palate, abnormal forebrain structures, polydactyly, congenital heart disease. Death usually occurs within 1 year of birth.

Puberty (13).

**Cri-du-chat syndrome**

Congenital deletion of short arm of chromosome 5 (46,XX or XY, 5p-).  
Findings: microcephaly, severe mental retardation, high-pitched crying/mewing, epicanthal folds, cardiac abnormalities.

*Cri du chat* = cry of the cat.

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<b>22q11 syndromes</b>	Cleft palate, Abnormal facies, Thymic aplasia → T-cell deficiency, Cardiac defects, Hypocalcemia 2° to parathyroid aplasia, microdeletion at chromosome 22q11. Variable presentation as DiGeorge syndrome (thymic, parathyroid, and cardiac defects) or velocardiofacial syndrome (palate, facial, and cardiac defects).	CATCH-22.
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<b>Fetal alcohol syndrome</b>	Newborns of mothers who consumed significant amounts of alcohol (teratogen) during pregnancy (highest risk at 3–8 weeks) have ↑ incidence of congenital abnormalities, including pre- and postnatal developmental retardation, microcephaly, facial abnormalities, limb dislocation, and heart and lung fistulas. Mechanism may include inhibition of cell migration. The number one cause of congenital malformations in the United States.	
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# Embryology

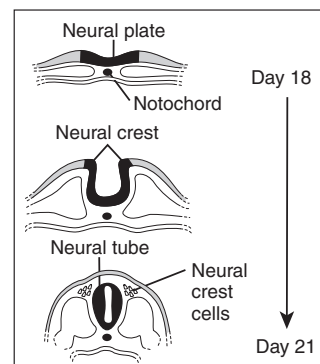
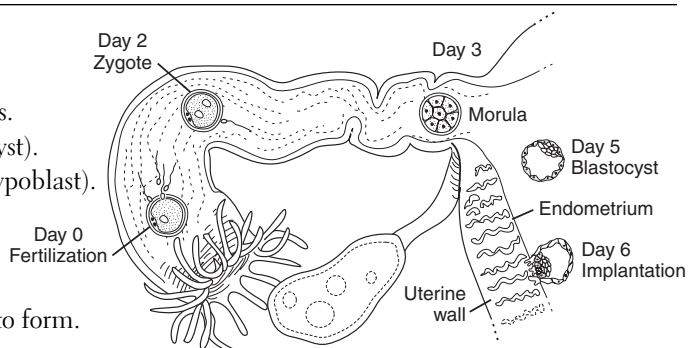
*“Zygote. This cell, formed by the union of an ovum and a sperm, represents the beginning of a human being.”*

—Keith Moore and Vid Persaud,  
*Before We Are Born*

Embryology is traditionally one of the higher-yield areas within anatomy. This topic can be crammed closer to the exam date. Many questions focus on underlying mechanisms of congenital malformations (e.g., failure of fusion of the maxillary and medial nasal processes leading to cleft palate).

**Fetal landmarks**

Day 0	Fertilization by sperm, initiating embryogenesis.
Within week 1	Implantation (as a blastocyst).
Within week 2	Bilaminar disk (epiblast:hypoblast).
Within week 3	Gastrulation. Primitive streak, notochord, and neural plate begin to form.
Weeks 3–8	Neural tube formed. Organogenesis. Extremely susceptible to teratogens.
Week 4	Heart begins to beat: 4 chambers in week 4.
Week 8	Upper and lower limb buds begin to form.
Week 10	Fetal movement; fetus looks like a baby. Genitalia have male/female characteristics.
Alar plate	Sensory
Basal plate	Motor

**Early development**

Rule of 2's for 2nd week	2 germ layers (bilaminar disk): epiblast, hypoblast. 2 cavities: amniotic cavity, yolk sac. 2 components to placenta: cytotrophoblast, syncytiotrophoblast.	The epiblast (precursor to ectoderm) invaginates to form primitive streak. Cells from the primitive streak give rise to both intraembryonic mesoderm and endoderm.
Rule of 3's for 3rd week	3 germ layers (gastrula): ectoderm, mesoderm, endoderm.	

**Embryologic derivatives****Ectoderm**

Surface ectoderm	Adenohypophysis; lens of eye; epithelial linings of skin, ear, eye, and nose; epidermis.
Neuroectoderm	Neurohypophysis, CNS neurons, oligodendrocytes, astrocytes, ependymal cells, pineal gland.
Neural crest	ANS, dorsal root ganglia, cranial nerves, melanocytes, chromaffin cells of adrenal medulla, enterochromaffin cells, pia and arachnoid, celiac ganglion, Schwann cells, odontoblasts, parafollicular (C) cells of thyroid, laryngeal cartilage, bones of the skull.

**Endoderm**

Gut tube epithelium and derivatives (e.g., lungs, liver, pancreas, thymus, parathyroid, thyroid follicular cells).

**Notochord**

Induces ectoderm to form neuroectoderm (neural plate). Its postnatal derivative is the nucleus pulposus of the intervertebral disk.

**Mesoderm**

Dura mater, connective tissue, muscle, bone, cardiovascular structures, lymphatics, blood, urogenital structures, serous linings of body cavities (e.g., peritoneal), spleen, adrenal cortex, kidneys.

Mesodermal defects = **VACTERL**: Vertebral defect, Anal atresia, Cardiac defects, Tracheo-Esophageal fistula, Renal defects, Limb defects (bone and muscle).

**Common congenital malformations**

1. Heart defects
2. Hypospadias
3. Cleft lip (with or without cleft palate)
4. Congenital hip dislocation
5. Spina bifida
6. Anencephaly
7. Pyloric stenosis

Associated with projectile vomiting.

**Teratogens**

Most susceptible in 3rd–8th weeks (organogenesis) of pregnancy.

**Examples**

Alcohol

ACE inhibitors

Cocaine

Diethylstilbestrol (DES)

Iodide

13-*cis*-retinoic acid

Thalidomide

Tobacco

Warfarin, x-rays, anticonvulsants

Fetal infections can also cause congenital malformations. (Other medications contraindicated in pregnancy are shown in the pharmacology section.)

**Effects on fetus**

Birth defects and mental retardation (leading cause); fetal alcohol syndrome

Renal damage

Abnormal fetal development and fetal addiction

Vaginal clear cell adenocarcinoma

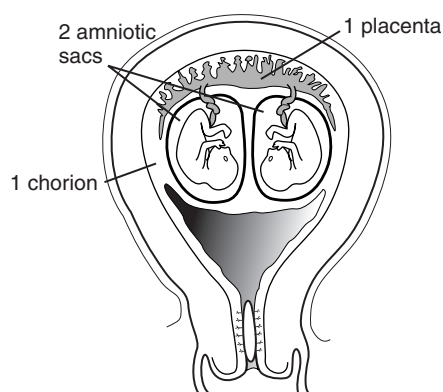
Congenital goiter or hypothyroidism

Extremely high risk for birth defects

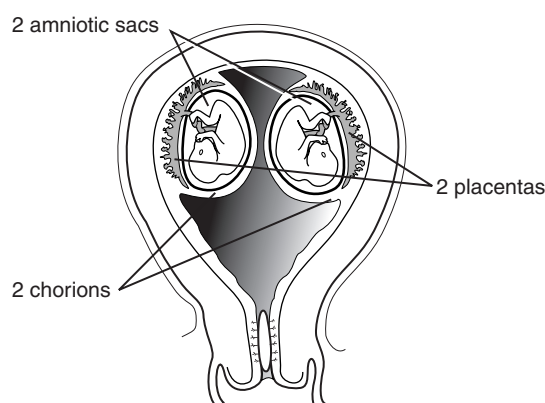
Limb defects (“flipper” limbs)

Preterm labor, placental problems, attention-deficit hyperactivity disorder (ADHD)

Multiple anomalies

**Twinning****Monozygotic**

1 zygote splits evenly to develop 2 amniotic sacs with a single common chorion and placenta.

**Dizygotic (fraternal) or monozygotic**

Dizygotes develop individual placentas, chorions, and amniotic sacs.

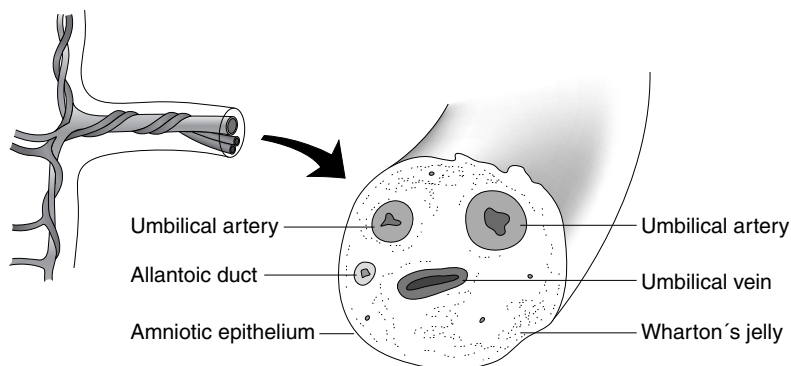
Monozygotes develop 2 placentas (separate/fused), chorions, and amniotic sacs.

**Umbilical cord**

Contains 2 umbilical arteries, which return deoxygenated blood from fetal internal iliac arteries, and 1 umbilical vein, which supplies oxygenated blood from the placenta to the fetus.

Allantoic duct removes nitrogenous waste (from fetal bladder, like a urethra).

Single umbilical artery is associated with congenital and chromosomal anomalies.

**Heart embryology****Embryonic structure**

Truncus arteriosus

Bulbus cordis

Primitive ventricle

Primitive atria

Left horn of sinus venosus (SV)

Right horn of SV

Right common cardinal vein and right anterior cardinal vein

**Gives rise to**

Ascending aorta and pulmonary trunk

Smooth parts of left and right ventricle

Trabeculated parts of left and right ventricle

Trabeculated left and right atrium

Coronary sinus

Smooth part of right atrium

SVC

**Fetal erythropoiesis**

Fetal erythropoiesis occurs in:

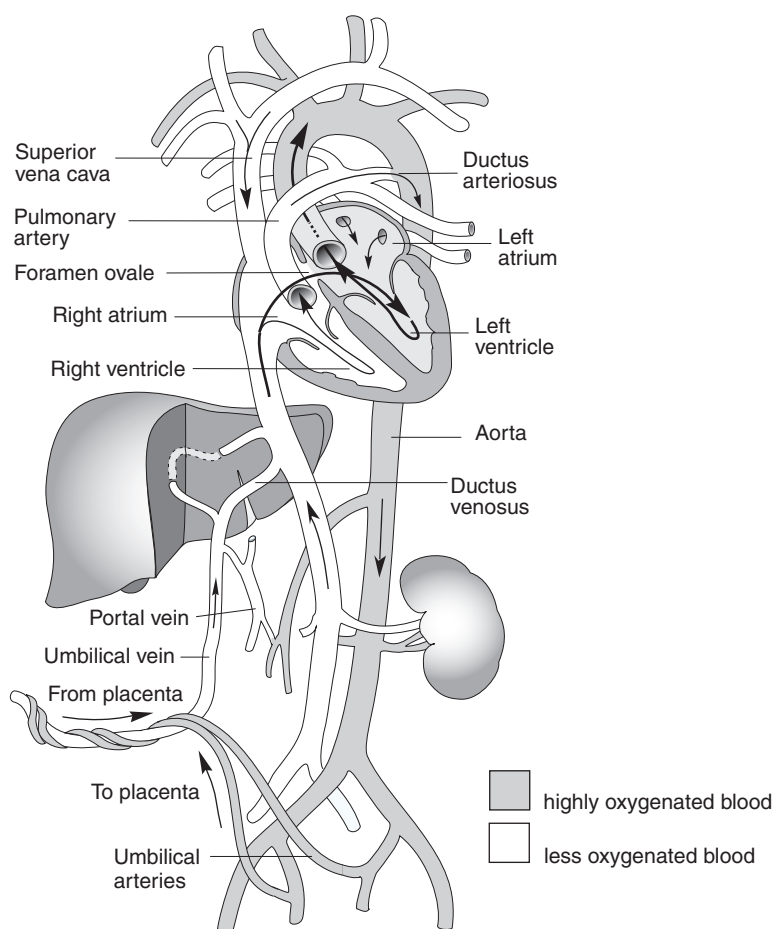
1. Yolk sac (3–8 wk)
2. Liver (6–30 wk)
3. Spleen (9–28 wk)
4. Bone marrow (28 wk onward)

Young Liver Synthesizes Blood.

Fetal hemoglobin =  $\alpha_2\gamma_2$ .

Adult hemoglobin =  $\alpha_2\beta_2$ .

## Fetal circulation



(Adapted, with permission, from Ganong WF. *Review of Medical Physiology*, 19th ed. Stamford, CT: Appleton & Lange, 1999:600.)

Blood in umbilical vein is  $\approx 80\%$  saturated with  $O_2$ .

3 important shunts:

1. Most oxygenated blood reaching the heart via the IVC is diverted through the **foramen ovale** and pumped out the aorta to the head.
2. Deoxygenated blood from the SVC is expelled into the pulmonary artery and **ductus arteriosus** to the lower body of the fetus.
3. Blood entering the fetus through the umbilical vein is conducted via the **ductus venosus** into the IVC.

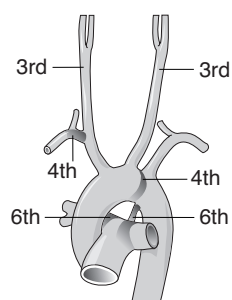
At birth, infant takes a breath;  
 $\downarrow$  resistance in pulmonary vasculature causes  $\uparrow$  left atrial pressure vs. right atrial pressure; foramen ovale closes;  $\uparrow$  in  $O_2$  leads to  $\downarrow$  in prostaglandins, causing closure of ductus arteriosus. Indomethacin closes the PDA. Prostaglandins keep a patent PDA open.

## Fetal-postnatal derivatives

1. Umbilical vein—ligamentum teres hepatis
2. Umbilical arteries—**media**L umbilical ligaments
3. Ductus arteriosus—ligamentum arteriosum
4. Ductus venosus—ligamentum venosum
5. Foramen ovale—fossa ovalis
6. **Alla**Ntois—urachus—**media**N umbilical ligament
7. Notochord—nucleus pulposus of intervertebral disk

The urachus is the part of the allantoic duct between the bladder and the umbilicus. Urachal cyst or sinus is a remnant.

## Aortic arch derivatives

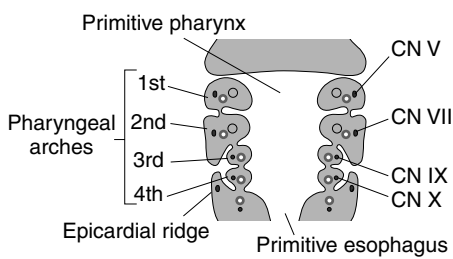


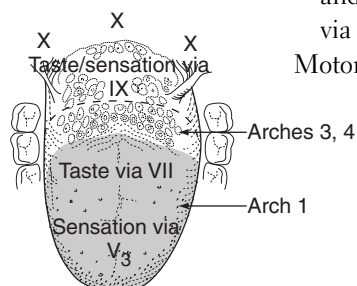
- 1st—part of **MAX**illary artery.
- 2nd—**Stapedial** artery and hyoid artery.
- 3rd—common **Carotid** artery and proximal part of internal carotid artery.
- 4th—on left, aortic arch; on right, proximal part of right subclavian artery.
- 6th—proximal part of pulmonary arteries and (on left only) ductus arteriosus.

1st arch is **MAX**imal.  
 Second = **Stapedial**.  
**C** is 3rd letter of alphabet.

4th arch (4 limbs) = systemic.  
 6th arch = pulmonary and the pulmonary-to-systemic shunt (ductus arteriosus).



<b>Branchial apparatus</b>	Composed of branchial clefts, arches, and pouches. Branchial clefts are derived from ectoderm. Branchial arches are derived from mesoderm and neural crests. Branchial pouches are derived from endoderm.	<b>CAP</b> covers outside from inside (Clefts = ectoderm, Arches = mesoderm, Pouches = endoderm). Branchial apparatus is also called pharyngeal apparatus. Clefts are also called grooves.
<b>Branchial arch 1 derivatives</b>	Meckel's cartilage: Mandible, Malleus, incus, sphenomandibular ligament. Muscles: Muscles of Mastication (temporalis, Masseter, lateral and Medial pterygoids), Mylohyoid, anterior belly of digastric, tensor tympani, tensor veli palatini, anterior ⅔ of tongue. Nerve: CN V <sub>2</sub> and CN V <sub>3</sub> .	
<b>Branchial arch 2 derivatives</b>	Reichert's cartilage: Stapes, Styloid process, lesser horn of hyoid, Stylohyoid ligament. Muscles: muscles of facial expression, Stapedius, Stylohyoid, posterior belly of digastric. Nerve: CN VII.	
<b>Branchial arch 3 derivatives</b>	Cartilage: greater horn of hyoid. Muscle: stylopharyngeus. Nerve: CN IX.	Think of pharynx: stylopharyngeus innervated by glossopharyngeal nerve.
<b>Branchial arches 4–6 derivatives</b>	Cartilages: thyroid, cricoid, arytenoids, corniculate, cuneiform. Muscles (4th arch): most pharyngeal constrictors, cricothyroid, levator veli palatini. Muscles (6th arch): all intrinsic muscles of larynx except cricothyroid. Nerve: 4th arch—CN X (superior laryngeal branch); 6th arch—CN X (recurrent laryngeal branch).	Arches 3 and 4 form posterior ⅓ of tongue. Arch 5 makes no major developmental contributions.
<b>Branchial arch innervation</b>	Arch 1 derivatives supplied by CN V <sub>2</sub> and V <sub>3</sub> . Arch 2 derivatives supplied by CN VII. Arch 3 derivatives supplied by CN IX. Arch 4 and 6 derivatives supplied by CN X.	 <p>The diagram illustrates the primitive pharynx and esophagus. The primitive pharynx is shown as a central cavity. The first four pharyngeal arches are labeled on the left: 1st, 2nd, 3rd, and 4th. The primitive esophagus is shown as a tube extending from the pharynx. The diagram also shows the associated nerves: CN V (trigeminal) for the 1st arch, CN VII (facial) for the 2nd arch, CN IX (glossopharyngeal) for the 3rd arch, and CN X (vagus) for the 4th arch. The epicardial ridge is also indicated.</p>

**Tongue development**

1st branchial arch forms anterior  $\frac{2}{3}$  (thus sensation via CN V<sub>3</sub>, taste via CN VII).  
 3rd and 4th arches form posterior  $\frac{1}{3}$  (thus sensation and taste mainly via CN IX, extreme posterior via CN X).  
 Motor innervation is via CN XII.

Taste is CN VII, IX, X (solitary nucleus); pain is CN V<sub>3</sub>, IX, X; motor is CN XII.

**Branchial cleft derivatives**

1st cleft develops into external auditory meatus.  
 2nd through 4th clefts form temporary cervical sinuses, which are obliterated by proliferation of 2nd arch mesenchyme.

Persistent cervical sinus can lead to a branchial cyst in the lateral neck.  
 Thyroglossal duct cyst in midline neck.

**Ear development****Bones**

Malleus/incus—  
 1st arch

Stapes—2nd arch

**Muscles**

Tensor tympani (V<sub>3</sub>)—1st arch

Stapedius (VII)—2nd arch

**Miscellaneous**

External auditory meatus—  
 1st cleft

Eardrum, eustachian tube—1st branchial membrane (branchial membranes are located at junctions of clefts with pouches)

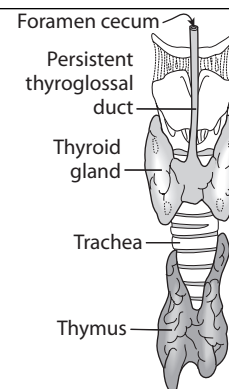
**Branchial pouch derivatives**

1st pouch develops into middle ear cavity, eustachian tube, mastoid air cells.  
 2nd pouch develops into epithelial lining of palatine tonsil.  
 3rd pouch (dorsal wings) develops into **inferior** parathyroids.  
 3rd pouch (ventral wings) develops into thymus.  
 4th pouch develops into **superior** parathyroids.

1st pouch contributes to endoderm-lined structures of ear.  
 3rd pouch contributes to 3 structures (thymus, left and right inferior parathyroids).  
 Aberrant development of 3rd and 4th pouches → DiGeorge syndrome → leads to T-cell deficiency (thymic aplasia) and hypocalcemia (failure of parathyroid development).

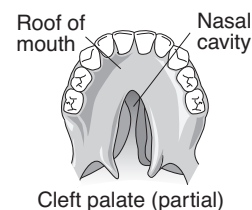
**Thyroid development**

Thyroid diverticulum arises from floor of primitive pharynx, descends into neck. Connected to tongue by thyroglossal duct, which normally disappears but may persist as pyramidal lobe of thyroid. Foramen cecum is normal remnant of thyroglossal duct. Most common ectopic thyroid tissue site is the tongue.

**Cleft lip and cleft palate**

Cleft lip

Cleft lip—failure of fusion of the maxillary and medial nasal processes (formation of 1° palate).  
Cleft palate—failure of fusion of the lateral palatine processes, the nasal septum, and/or the median palatine process (formation of 2° palate).

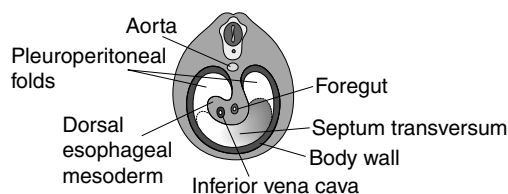


Cleft palate (partial)

**Diaphragm embryology**

Diaphragm is derived from:

1. Septum transversum
2. Pleuroperitoneal folds
3. Body wall
4. Dorsal mesentery of esophagus

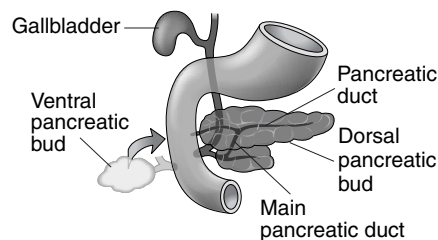
**Several Parts Build Diaphragm.**

Diaphragm descends during development but maintains innervation from above C3–C5. “C3, 4, 5 keeps the diaphragm alive.”

Abdominal contents may herniate into the thorax due to incomplete development (hiatal hernia).

**Pancreas and spleen embryology**

Pancreas is derived from the foregut. Ventral pancreatic bud becomes pancreatic head, uncinate process (lower half of head), and main pancreatic duct. Dorsal pancreatic bud becomes everything else (body, tail, isthmus, and accessory pancreatic duct).  
Spleen arises from dorsal mesentery but is supplied by artery of foregut.  
Annular pancreas—ventral and dorsal pancreatic buds abnormally encircle duodenum; forms a ring of pancreatic tissue that may cause duodenal narrowing.



**GI embryology**

1. Foregut—pharynx to duodenum
2. Midgut—duodenum to transverse colon
3. Hindgut—distal transverse colon to rectum

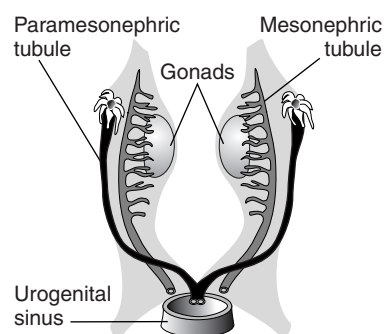
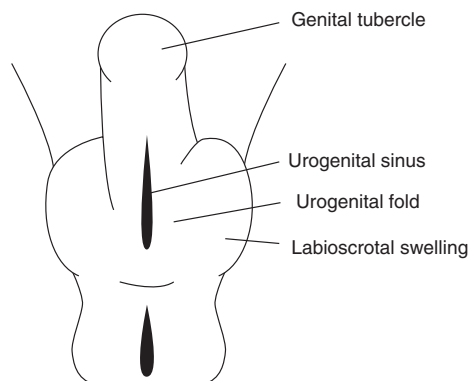
**Kidney embryology**

1. Pronephros—week 4
2. Mesonephros—first trimester
3. Metanephros—permanent

**Genital ducts**

Mesonephric  
(wolffian) duct  
Paramesonephric  
(müllerian) duct

Develops into Seminal vesicles, Epididymis, Ejaculatory duct, and Ductus deferens.  
Develops into fallopian tube, uterus, and part of vagina.  
Müllerian inhibiting substance secreted by testes suppresses development of paramesonephric ducts in males.  
↑ androgens cause development of mesonephric ducts.

**SEED.****Male/female genital homologues****Male**

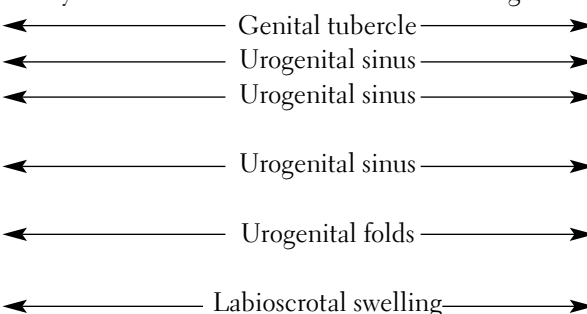
Glans penis  
Corpus spongiosum  
Bulbourethral glands  
(of Cowper)  
Prostate gland  
Ventral shaft of penis  
(penile urethra)  
Scrotum

Dihydrotestosterone

Estrogen

**Female**

Glans clitoris  
Vestibular bulbs  
Greater vestibular glands  
(of Bartholin)  
Urethral and paraurethral glands  
(of Skene)  
Labia minora  
Labia majora



# HIGH-YIELD PRINCIPLES IN

# Microbiology

*“What lies behind us and what lies ahead of us are tiny matters compared to what lives within us.”*

—Oliver Wendell Holmes

This high-yield material covers the basic concepts of microbiology. The emphasis in previous examinations has been approximately 40% bacteriology (20% basic, 20% quasi-clinical), 25% immunology, 25% virology (10% basic, 15% quasi-clinical), 5% parasitology, and 5% mycology. Learning the distinguishing characteristics, target organs, and method of spread of—as well as relevant laboratory tests for—major pathogens can improve your score substantially.

- ▶ High-Yield Clinical Vignettes
- ▶ Clinical Bacteriology
- ▶ Bacteriology
- ▶ Mycology
- ▶ Parasitology
- ▶ Virology
- ▶ Systems
- ▶ Antimicrobials

## MICROBIOLOGY—HIGH-YIELD CLINICAL VIGNETTES

■ Alcoholic vomits gastric contents and develops foul-smelling sputum.	What organisms are most likely?	Anaerobes.
■ Middle-age male presents with acute-onset monoarticular joint pain and bilateral Bell's palsy.	What is the likely disease and how did he get it?	Lyme disease; bite from <i>Ixodes</i> tick.
■ UA of patient shows WBC casts.	What is the diagnosis?	Pyelonephritis.
■ Patient presents with "rose gardener's" scenario (thorn prick with ulcers along lymphatic drainage).	What is the infectious bug?	<i>Sporothrix schenckii</i> .
■ 25-year-old medical student has a burning feeling in his gut after meals. Biopsy of gastric mucosa shows gram-negative rods.	What is the likely organism?	<i>Helicobacter pylori</i> .
■ 32-year-old male has "cauliflower" skin lesions. Tissue biopsy shows broad-based budding yeasts.	What is the likely organism?	<i>Blastomyces</i> .
■ Breast-feeding woman suddenly develops redness and swelling of her right breast. On examination, it is found to be a fluctuant mass.	What is the diagnosis?	Mastitis caused by <i>S. aureus</i> .
■ 20-year-old college student presents with lymphadenopathy, fever, and hepatosplenomegaly. His serum agglutinates sheep RBCs.	What cell is infected?	B cell (EBV; infectious mononucleosis).
■ One hour after eating custard at a picnic, a whole family began to vomit. After 10 hours, they were better.	What is the organism?	<i>S. aureus</i> (produces preformed enterotoxin).
■ Infant becomes flaccid after eating honey.	What organism is implicated, and what is the mechanism of action?	<i>Clostridium botulinum</i> ; inhibited release of ACh.
■ Man presents with squamous cell carcinoma of the penis.	He had exposure to what virus?	HPV.
■ Patient develops endocarditis three weeks after receiving a prosthetic heart valve.	What organism is suspected?	<i>S. epidermidis</i> or <i>S. aureus</i> .

- |                                                                                                                                                                                       |                                    |                                          |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------|------------------------------------------|
| ■ 55-year-old man who is a smoker and a heavy drinker presents with a new cough and flulike symptoms. Gram stain shows no organisms; silver stain of sputum shows gram-negative rods. | What is the diagnosis?             | <i>Legionella</i> pneumonia.             |
| ■ After taking clindamycin, patient develops toxic megacolon and diarrhea.                                                                                                            | What is the mechanism of diarrhea? | <i>Clostridium difficile</i> overgrowth. |

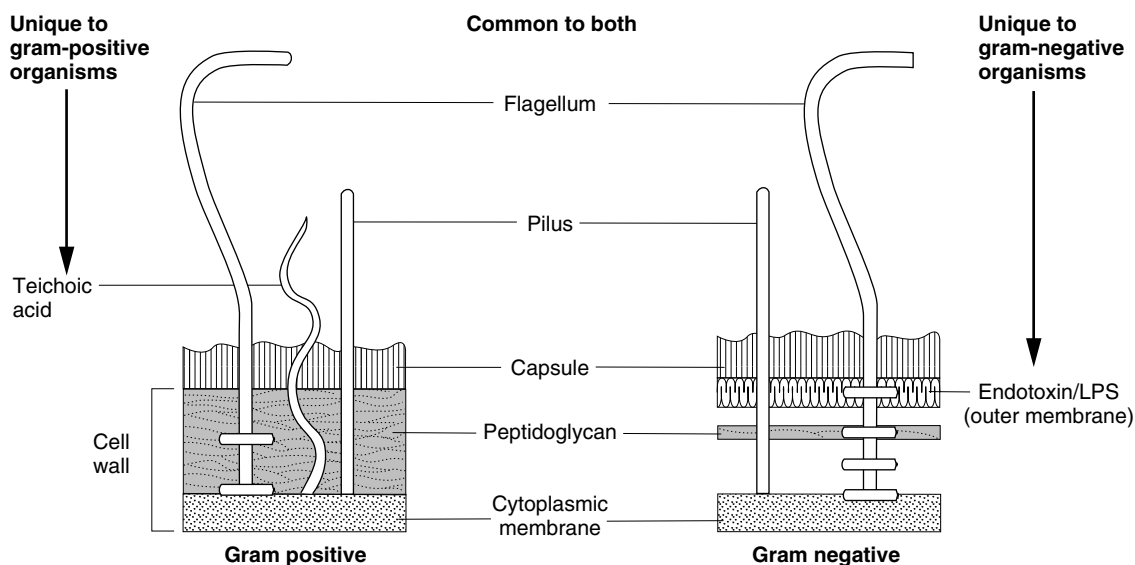
## ► MICROBIOLOGY—CLINICAL BACTERIOLOGY

**Bacterial structures**

Structure	Function	Chemical composition
Peptidoglycan	Gives rigid support, protects against osmotic pressure.	Sugar backbone with cross-linked peptide side chains.
Cell wall/cell membrane (gram positives)	Major surface antigen.	Teichoic acid induces TNF and IL-1.
Outer membrane (gram negatives)	Site of endotoxin (lipopolysaccharide); major surface antigen.	Lipid A induces TNF and IL-1; polysaccharide is the antigen.
Plasma membrane	Site of oxidative and transport enzymes.	Lipoprotein bilayer.
Ribosome	Protein synthesis.	50S and 30S subunits.
Periplasm	Space between the cytoplasmic membrane and outer membrane in gram-negative bacteria.	Contains many hydrolytic enzymes, including $\beta$ -lactamases.
Capsule	Protects against phagocytosis.	Polysaccharide (except <i>Bacillus anthracis</i> , which contains D-glutamate). Glycoprotein.
Pilus/fimbria	Mediates adherence of bacteria to cell surface; sex pilus forms attachment between 2 bacteria during conjugation.	
Flagellum	Motility.	Protein.
Spore	Provides resistance to dehydration, heat, and chemicals.	Keratin-like coat; dipicolinic acid.
Plasmid	Contains a variety of genes for antibiotic resistance, enzymes, and toxins.	DNA.
Glycocalyx	Mediates adherence to surfaces, especially foreign surfaces (e.g., indwelling catheters).	Polysaccharide.
IgA proteases	Allow some organisms to colonize mucosal surfaces: <i>S. pneumoniae</i> , <i>N. meningitidis</i> , <i>N. gonorrhoeae</i> , <i>H. influenzae</i> .	



## Cell walls



(Adapted, with permission, from Levinson W, Jawetz E. *Medical Microbiology and Immunology: Examination and Board Review*, 9th ed. New York: McGraw-Hill, 2006:7.)

### Gram stain limitations

These bugs do not Gram stain well:

*Treponema* (too thin to be visualized).

*Rickettsia* (intracellular parasite).

*Mycobacteria* (high-lipid-content cell wall requires acid-fast stain).

*Mycoplasma* (no cell wall).

*Legionella pneumophila* (primarily intracellular).

*Chlamydia* (intracellular parasite; lacks muramic acid in cell wall).

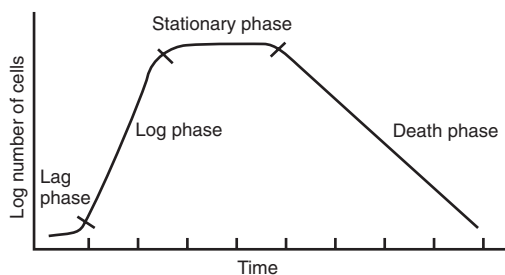
These Rascals May Microscopically Lack Color.

*Treponemes*—darkfield microscopy and fluorescent antibody staining.

*Mycobacteria*—acid fast.

*Legionella*—silver stain.

### Bacterial growth curve



(Adapted, with permission, from Levinson W. *Medical Microbiology and Immunology: Examination and Board Review*, 9th ed. New York: McGraw-Hill, 2006:15.)

Lag—metabolic activity without division.

Log—rapid cell division.

Stationary—nutrient depletion slows growth.

Death—prolonged nutrient depletion and buildup of waste products lead to death.

► MICROBIOLOGY—CLINICAL BACTERIOLOGY (*continued*)**Main features of exotoxins and endotoxins**

Property	Exotoxin	Endotoxin
Source	Certain species of some gram-positive and gram-negative bacteria	Cell wall of most gram-negative bacteria
Secreted from cell	Yes	No
Chemistry	Polypeptide	Lipopolysaccharide
Location of genes	Plasmid or bacteriophage	Bacterial chromosome
Toxicity	High (fatal dose on the order of 1 µg)	Low (fatal dose on the order of hundreds of micrograms)
Clinical effects	Various effects (see text)	Fever, shock
Mode of action	Various modes (see text)	Includes TNF and IL-1
Antigenicity	Induces high-titer antibodies called antitoxins	Poorly antigenic
Vaccines	Toxoids used as vaccines	No toxoids formed and no vaccine available
Heat stability	Destroyed rapidly at 60°C (except staphylococcal enterotoxin)	Stable at 100°C for 1 hour
Typical diseases	Tetanus, botulism, diphtheria	Meningococcemia, sepsis by gram-negative rods

(Adapted, with permission, from Levinson W. *Medical Microbiology and Immunology: Examination and Board Review*, 8th ed. New York: McGraw-Hill, 2004:39.)

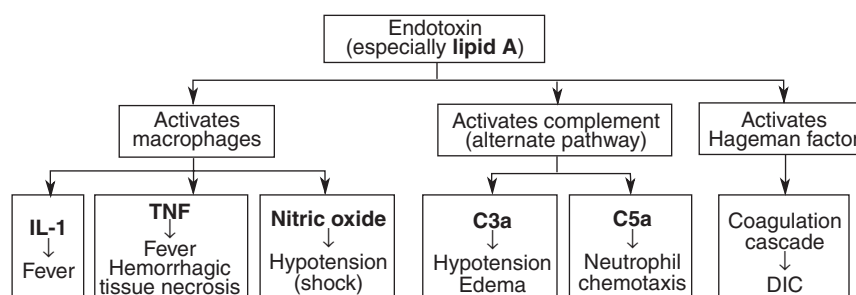
**Bugs with exotoxins**

<b>Superantigens</b>	Bind directly to MHC II and T-cell receptor, activating large numbers of T cells to stimulate release of IFN- $\gamma$ and IL-2.
<i>S. aureus</i>	TSST-1 causes toxic shock syndrome (fever, rash, shock). Enterotoxins cause food poisoning.
<i>S. pyogenes</i>	Scarlet fever–erythrogenic toxin causes toxic shock–like syndrome.
<b>ADP ribosylating A-B toxins</b>	Interfere with host cell function. B (binding) component binds to a receptor on surface of host cell, enabling endocytosis. A (active) component then attaches an ADP-ribosyl to a host cell protein (ADP ribosylation), altering protein function.
<i>Corynebacterium diphtheriae</i>	Inactivates elongation factor (EF-2) (similar to <i>Pseudomonas</i> exotoxin A); causes pharyngitis and “pseudomembrane” in throat.
<i>Vibrio cholerae</i>	ADP ribosylation of G protein stimulates adenyl cyclase; increases pumping of Cl <sup>-</sup> and H <sub>2</sub> O into gut; causes voluminous rice-water diarrhea.
<i>E. coli</i>	Heat-labile toxin stimulates adenylate cyclase (cholera-like mechanism), causing watery diarrhea. Heat-stable toxin stimulates guanylate cyclase. “Labile like the air, stable like the ground.”
<i>Bordetella pertussis</i>	Stimulates adenylate cyclase; causes whooping cough; inhibits chemokine receptor, causing lymphocytosis.
<b>Other toxins</b>	
<i>Clostridium perfringens</i>	$\alpha$ toxin causes gas gangrene; get double zone of hemolysis on blood agar.
<i>C. tetani</i>	Blocks the release of inhibitory neurotransmitter glycine; causes “lockjaw.”
<i>C. botulinum</i>	Blocks the release of acetylcholine; causes anticholinergic symptoms, CNS paralysis especially cranial nerves; spores found in canned food, honey (causes floppy baby).
<i>Bacillus anthracis</i>	I toxin in the toxin complex is an adenylate cyclase.
<i>Shigella</i>	Shiga toxin (also produced by <i>E. coli</i> O157:H7) cleaves host cell rRNA; also enhances cytokine release, causing HUS.
<i>S. pyogenes</i>	Streptolysin O is a hemolysin; antigen for ASO antibody in rheumatic fever.

**Endotoxin**

A lipopolysaccharide found in cell wall of gram-negative bacteria.

N-dotoxin is an integral part of gram-negative cell wall.  
Endotoxin is heat stable.



(Adapted, with permission, from Levinson W, Jawetz E. *Medical Microbiology and Immunology: Examination and Board Review*, 6th ed. New York: McGraw-Hill, 2000:39.)

► MICROBIOLOGY—CLINICAL BACTERIOLOGY (*continued*)**Fermentation patterns of *Neisseria***

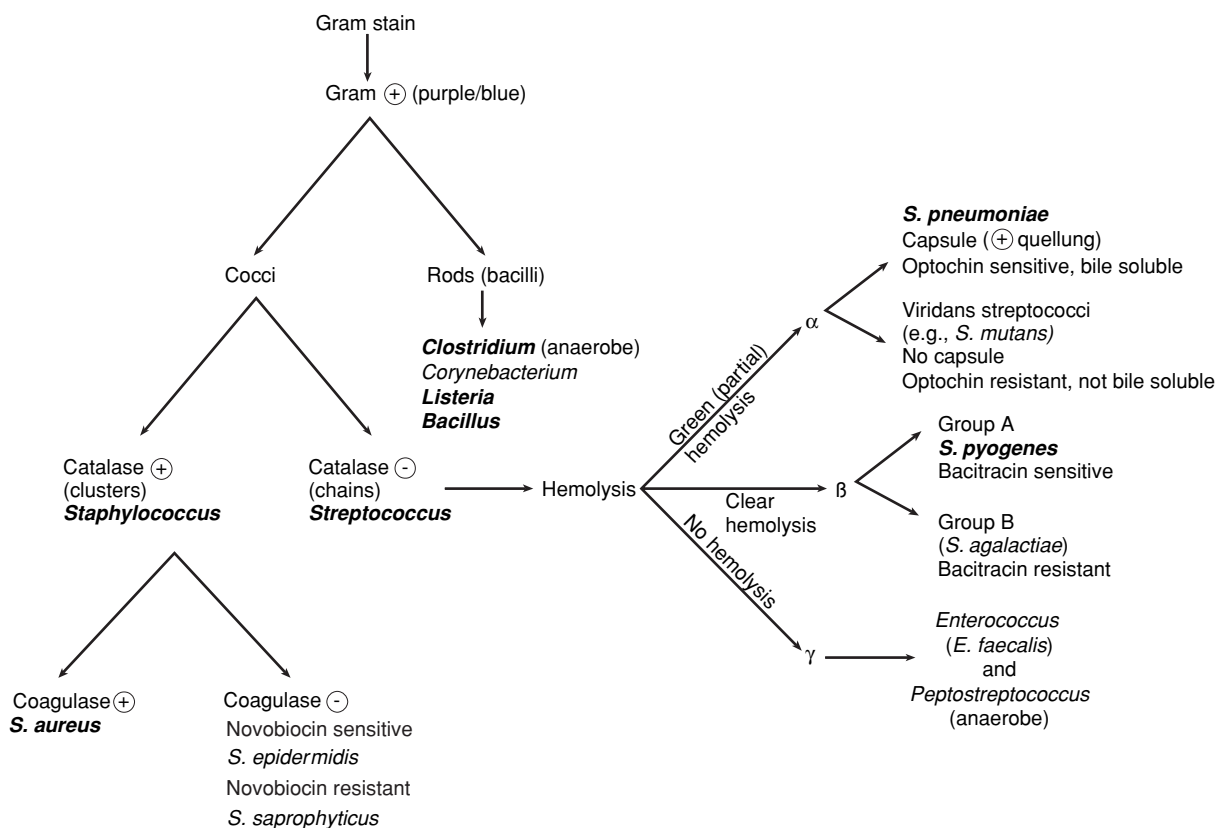
The pathogenic *Neisseria* species are differentiated on the basis of sugar fermentation (see Color Image 4).

**Menin**Gococci ferment Maltose and Glucose.  
Gonococci ferment Glucose.

**Pigment-producing bacteria**

*S. aureus*—yellow pigment.  
*Pseudomonas aeruginosa*—blue-green pigment.  
*Serratia marcescens*—red pigment.

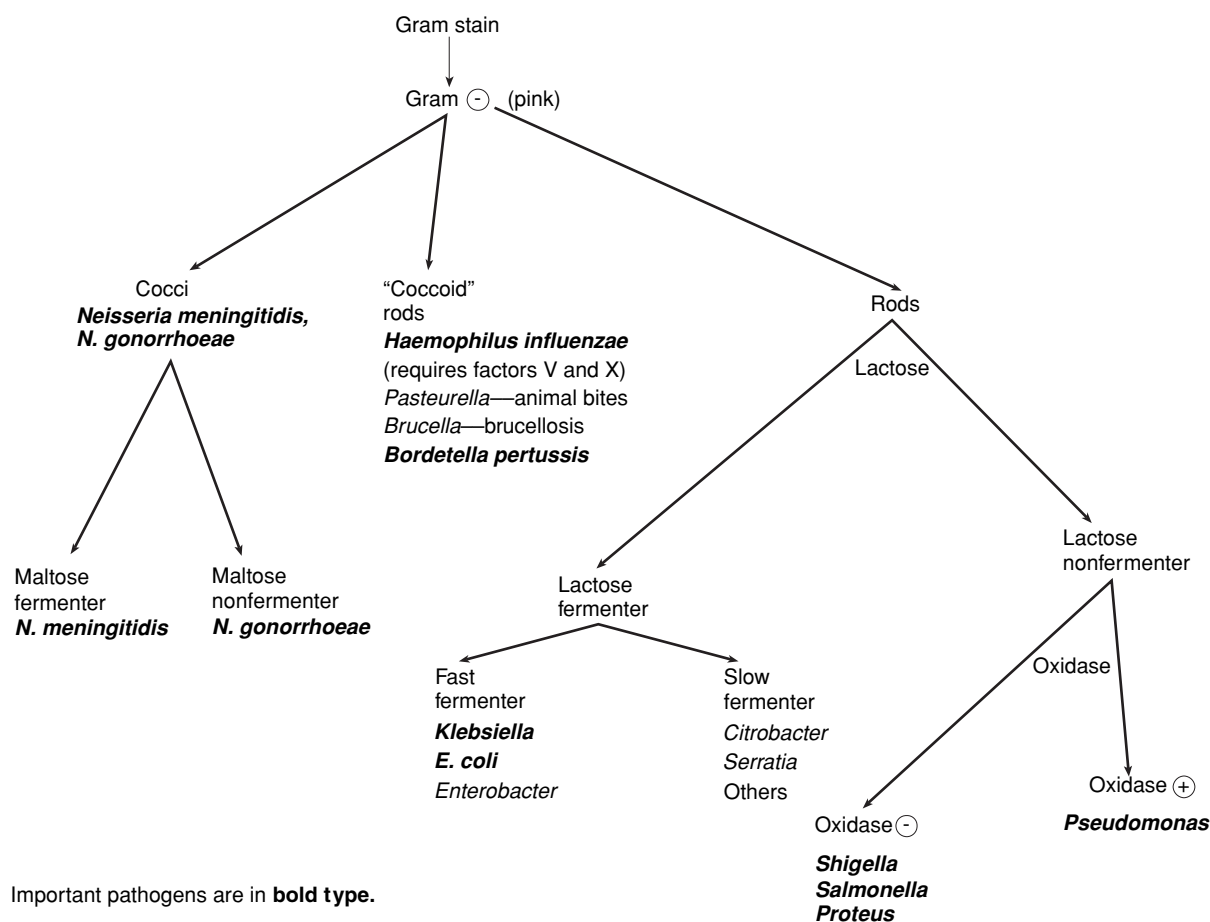
*Aureus* (Latin) = gold.  
*Serratia marcescens*—think red maraschino cherries!

**Gram-positive lab algorithm**

Important pathogens are in **bold type**.

Note: *Enterococcus* is either  $\alpha$ - or  $\gamma$ -hemolytic.

## Gram-negative lab algorithm



Important pathogens are in **bold type**.

## Special culture requirements

Bug	Media used for isolation
<i>H. influenzae</i>	Chocolate agar with factors V (NAD) and X (hematin)
<i>N. gonorrhoeae</i>	Thayer-Martin media
<i>B. pertussis</i>	Bordet-Gengou (potato) agar
<i>C. diphtheriae</i>	Tellurite plate, Löffler's medium, blood agar
<i>M. tuberculosis</i>	Löwenstein-Jensen agar
Lactose-fermenting enterics	Pink colonies on MacConkey's agar
<i>Legionella</i>	Charcoal yeast extract agar buffered with increased iron and cysteine
Fungi	Sabouraud's agar

## Stains

Congo red	Amyloid; apple-green birefringence in polarized light (because of $\beta$ -pleated sheets).
Giemsa's	<i>Borrelia</i> , <i>Plasmodium</i> , trypanosomes, <i>Chlamydia</i> .
PAS (periodic acid-Schiff)	Stains glycogen, mucopolysaccharides; used to diagnose Whipple's disease.
Ziehl-Neelsen	Acid-fast bacteria.
India ink	<i>Cryptococcus neoformans</i> .
Silver stain	Fungi, PCP, <i>Legionella</i> .

► MICROBIOLOGY—CLINICAL BACTERIOLOGY (*continued*)**Bacterial genetics**

Transfer procedure	Transfer process	Types of cells involved	Nature of DNA transferred
Conjugation	Direct cell to cell DNA transfer	Prokaryotic	Chromosomal or plasmid
Transduction	Phage-mediated cell to cell DNA transfer	Prokaryotic	Any gene in generalized transduction; only certain genes in specialized transduction
Transformation	Purified DNA taken up by a cell	Prokaryotic or eukaryotic (e.g., human)	Any DNA
Transposition	DNA transfer to same or another chromosome or plasmid within a cell	Prokaryotic or eukaryotic	DNA sequences ("jumping genes")

(Adapted, with permission, from Levinson W. *Medical Microbiology and Immunology: Examination and Board Review*, 8th ed. New York: McGraw-Hill, 2004:19.)

**Lysogeny**

Genetic code for a bacterial toxin encoded in a lysogenic phage.

Botulinum toxin

Cholera toxin

Diphtheria toxin

Erythrogenic toxin of *Streptococcus pyogenes*

## ► MICROBIOLOGY—BACTERIOLOGY

**Obligate aerobes**

Use an O<sub>2</sub>-dependent system to generate ATP.

Examples include *Nocardia*, *Pseudomonas aeruginosa*, *Mycobacterium tuberculosis*, and *Bacillus*.

*M. tuberculosis* has a predilection for the apices of the lung, which have the highest PO<sub>2</sub>.

**Nagging Pests Must Breathe.**

*P. AERuginosa* is an **AERobe** seen in burn wounds, nosocomial pneumonia, and pneumonias in cystic fibrosis patients.

**Obligate anaerobes**

Examples include *Clostridium*, *Bacteroides*, and *Actinomyces*. They lack catalase and/or superoxide dismutase and thus are susceptible to oxidative damage. Generally foul smelling (short-chain fatty acids), are difficult to culture, and produce gas in tissue (CO<sub>2</sub> and H<sub>2</sub>).

Anaerobes are normal flora in GI tract, pathogenic elsewhere. AminO<sub>2</sub>glycosides are ineffective against anaerobes because these antibiotics require O<sub>2</sub> to enter into bacterial cell.

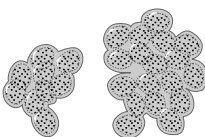
**Intracellular bugs**

Obligate intracellular *Rickettsia*, *Chlamydia*. Can't make own ATP.

Stay inside (cells) when it is **Really Cold**.

Facultative intracellular *Salmonella*, *Neisseria*, *Brucella*, *Mycobacterium*, *Listeria*, *Francisella*, *Legionella*, *Yersinia*.

**Some Nasty Bugs May Live FacultativeLY.**

<b>Encapsulated bacteria</b>	<p>Examples are <i>Streptococcus pneumoniae</i>, <i>Haemophilus influenzae</i> (especially B serotype), <i>Neisseria meningitidis</i>, and <i>Klebsiella pneumoniae</i>.</p> <p>Polysaccharide capsule is an antiphagocytic virulence factor.</p> <p>Positive <b>quellung</b> reaction—if encapsulated bug is present, capsule <b>swells</b> when specific anticapsular antisera are added.</p>	<p>Capsule serves as antigen in vaccines (Pneumovax, <i>H. influenzae</i> B, meningococcal vaccines). Conjugation with protein increases immunogenicity and T-cell dependent response.</p> <p><b>Quellung</b> = capsular “swelling.”</p>
<b>Spores: bacterial</b>	<p>Only certain gram-positive rods form spores when nutrients are limited. Spores are highly resistant to destruction by heat and chemicals. Have dipicolinic acid in their core. Have no metabolic activity. Must autoclave to kill spores (as is done to surgical equipment).</p>	<p>Gram-positive soil bugs ≈ spore formers (<i>Bacillus anthracis</i>, <i>Clostridium perfringens</i>, <i>C. tetani</i>).</p>
<b>α-hemolytic bacteria</b>	<p>Include the following organisms:</p> <ol style="list-style-type: none"> <li>1. <i>Streptococcus pneumoniae</i> (catalase negative and optochin sensitive) (see Color Image 1)</li> <li>2. Viridans streptococci (catalase negative and optochin resistant)</li> </ol>	
<b>β-hemolytic bacteria</b>	<p>Include the following organisms:</p> <ol style="list-style-type: none"> <li>1. <i>Staphylococcus aureus</i> (catalase and coagulase positive)</li> <li>2. <i>Streptococcus pyogenes</i> (catalase negative and bacitracin sensitive)</li> <li>3. <i>Streptococcus agalactiae</i> (catalase negative and bacitracin resistant)</li> <li>4. <i>Listeria monocytogenes</i> (tumbling motility, meningitis in newborns, unpasteurized milk)</li> </ol>	
<b>Catalase/coagulase (gram-positive cocci)</b>	<p>Catalase degrades <math>H_2O_2</math>, an antimicrobial product of PMNs. <math>H_2O_2</math> is a substrate for myeloperoxidase. Staphylococci make catalase, whereas streptococci do not.</p> <p><i>S. aureus</i> makes coagulase, whereas <i>S. epidermidis</i> and <i>S. saprophyticus</i> do not.</p>	<p><b>Staph</b> make catalase because they have more “staff.” Bad staph (<i>aureus</i>, because <i>epidermidis</i> is skin flora) make coagulase and toxins.</p>
<b><i>Staphylococcus aureus</i></b> 	<p>Protein A (virulence factor) binds Fc-IgG, inhibiting complement fixation and phagocytosis.</p> <p>Causes:</p> <ol style="list-style-type: none"> <li>1. Inflammatory disease—skin infections, organ abscesses, pneumonia</li> <li>2. Toxin-mediated disease—toxic shock syndrome (TSST-1 toxin), scalded skin syndrome (exfoliative toxin), rapid-onset food poisoning (enterotoxins) (see Color Image 3)</li> </ol>	<p>TSST is a superantigen that binds to MHC II and T-cell receptor, resulting in polyclonal T-cell activation.</p> <p><i>S. aureus</i> food poisoning is due to ingestion of preformed toxin.</p> <p>Causes acute bacterial endocarditis, osteomyelitis.</p>

► MICROBIOLOGY—BACTERIOLOGY (*continued*)***Streptococcus pyogenes* (group A  $\beta$ -hemolytic streptococci) sequelae**

Causes:

1. Pyogenic—pharyngitis, cellulitis, impetigo
2. Toxigenic—scarlet fever, toxic shock syndrome
3. Immunologic—rheumatic fever, acute glomerulonephritis

Bacitracin sensitive. Antibody to **M protein** enhances host defenses against *S. pyogenes*.  
ASO titer detects recent *S. pyogenes* infection.

**PH**aryngitis gives you rheumatic “**PH**ever” and glomerulone**PH**ritis.  
No “**rheum**” for **SPECC**ulation:  
Subcutaneous nodules, Polyarthrit**is**, Erythema marginatum, Chorea, Carditis.

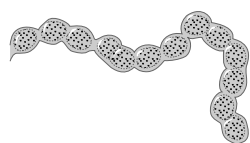
***Streptococcus pneumoniae***

Most common cause of:

Meningitis  
Otitis media (in children)  
Pneumonia  
Sinusitis

Encapsulated. IgA protease.

*S. pneumoniae* **MOPS** are Most **OP**tochin Sensitive.  
Pneumococcus is associated with “rusty” sputum, sepsis in sickle cell anemia and splenectomy.

**Group B streptococci**Bacitracin resistant,  $\beta$ -hemolytic; cause pneumonia, meningitis, and sepsis, mainly in babies.**Enterococci**

Enterococci (*Enterococcus faecalis* and *E. faecium*) are penicillin G resistant and cause UTI and subacute endocarditis. Lancefield group D includes the enterococci and the nonenterococcal group D streptococci. Lancefield grouping is based on differences in the C carbohydrate on the bacterial cell wall. Variable hemolysis.

Enterococci, hardier than nonenterococcal group D, can thus grow in 6.5% NaCl (lab test).  
*Entero* = intestine, *faecalis* = feces, *strepto* = twisted (chains), *coccus* = berry.

***Staphylococcus epidermidis***

Infects prosthetic devices and catheters. Component of normal skin flora; contaminates blood cultures.

**Viridans group streptococci**

Viridans streptococci are  $\alpha$ -hemolytic. They are normal flora of the oropharynx and cause dental caries (*Streptococcus mutans*) and subacute bacterial endocarditis (*S. sanguis*). Resistant to optochin, differentiating them from *S. pneumoniae*, which is  $\alpha$ -hemolytic but is optochin sensitive.

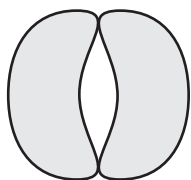
*Sanguis* (Latin) = blood.  
There is lots of blood in the heart (endocarditis).  
Viridans group strep live in the mouth because they are not afraid **of-the-chin** (**op-to-chin** resistant).



<b>Clostridia (with exotoxins)</b>	<p>Gram-positive, spore-forming, obligate anaerobic bacilli.</p> <p><i>Clostridium tetani</i> produces an exotoxin causing tetanus.</p> <p><i>C. botulinum</i> produces a preformed, heat-labile toxin that inhibits ACh release, causing botulism.</p> <p><i>C. perfringens</i> produces <math>\alpha</math> toxin (lecithinase) that causes myonecrosis, gas gangrene, or hemolysis.</p> <p><i>C. difficile</i> produces a cytotoxin, an exotoxin that kills enterocytes, causing pseudomembranous colitis. Often 2° to antibiotic use, especially clindamycin or ampicillin.</p>	<p><b>TET</b>anus is <b>TET</b>anic paralysis (blocks glycine release [inhibitory neurotransmitter]) from Renshaw cells in spinal cord.</p> <p><b>BOT</b>ulinum is from bad <b>BOT</b>tles of food and honey (causes a flaccid paralysis).</p> <p><b>PER</b>fringens <b>PER</b>forates a gangrenous leg.</p> <p><b>DI</b>fficile causes <b>DI</b>arrhea. Treat with metronidazole.</p>
<b>Diphtheria (and exotoxin)</b>	<p>Caused by <i>Corynebacterium diphtheriae</i> via exotoxin encoded by <math>\beta</math>-prophage. Potent exotoxin inhibits protein synthesis via ADP ribosylation of EF-2.</p> <p>Symptoms include pseudomembranous pharyngitis (grayish-white membrane) with lymphadenopathy.</p> <p>Lab diagnosis based on gram-positive rods with metachromatic granules.</p>	<p><i>Coryne</i> = club shaped.</p> <p>Grows on tellurite agar.</p> <p><b>ABCDEFGF</b>:</p> <p>ADP ribosylation</p> <p>Beta-prophage</p> <p><i>Corynebacterium</i></p> <p><i>Diphtheriae</i></p> <p>Elongation Factor 2</p> <p>Granules</p>
<b>Anthrax</b>	<p>Caused by <i>Bacillus anthracis</i>, a gram-positive, spore-forming rod that produces anthrax toxin.</p> <p>The only bacterium with a protein capsule.</p> <p>Contact → malignant pustule (painless ulcer); can progress to bacteremia and death.</p> <p>Inhalation of spores → flulike symptoms that rapidly progress to fever, pulmonary hemorrhage, and shock.</p>	<p>Black skin lesions—vesicular papules covered by black eschar.</p> <p>Woolsorters' disease—inhalation of spores from contaminated wool.</p>
<b>Actinomyces vs. Nocardia</b>	<p>Both are gram-positive rods forming long branching filaments resembling fungi.</p> <p><i>Actinomyces israelii</i>, a gram-positive anaerobe, causes oral/facial abscesses with "sulfur granules" that may drain through sinus tracts in skin. Normal oral flora.</p> <p><i>Nocardia asteroides</i>, a gram-positive and also a weakly acid-fast aerobe in soil, causes pulmonary infection in immunocompromised patients.</p>	<p><i>A. israelii</i> forms yellow "sulfur granules" in sinus tracts.</p> <p><b>SNAP</b>:</p> <p>Sulfa for</p> <p><i>Nocardia</i>;</p> <p><i>Actinomyces</i> use</p> <p>Penicillin</p>

► MICROBIOLOGY–BACTERIOLOGY (*continued*)**Penicillin and gram-negative bugs**

Gram-negative bugs are resistant to benzyl penicillin G but may be susceptible to penicillin derivatives such as ampicillin. The gram-negative outer membrane layer inhibits entry of penicillin G and vancomycin.

***Neisseria***

Gram-negative cocci.

**Gonococci**

No polysaccharide capsule

No maltose fermentation

No vaccine

Causes gonorrhea, septic arthritis, neonatal conjunctivitis, PID

**Meningococci**

Polysaccharide capsule

Maltose fermentation

Vaccine

Causes meningococemia and meningitis, Waterhouse-Friderichsen syndrome

***Haemophilus influenzae***

*HaEMOPhilus* causes Epiglottitis, Meningitis, Otitis media, and Pneumonia. Small gram-negative (coccobacillary) rod. Aerosol transmission. Most invasive disease caused by capsular type B. Produces IgA protease. Culture on chocolate agar requires factors **V** (NAD) and **X** (hematin) for growth. Treat meningitis with ceftriaxone. Rifampin prophylaxis in close contacts. Does not cause the flu (influenza virus does).

When a child has “flu,” mom goes to five (**V**) and dime (**X**) store to buy some chocolate. Vaccine contains type B capsular polysaccharide conjugated to diphtheria toxoid or other protein. Given between 2 and 18 months of age.

**Enterobacteriaceae**

Diverse family including *E. coli*, *Salmonella*, *Shigella*, *Klebsiella*, *Enterobacter*, *Serratia*, *Proteus*. All species have somatic (O) antigen (which is the polysaccharide of endotoxin). The capsular (K) antigen is related to the virulence of the bug. The flagellar (H) antigen is found in motile species. All ferment glucose and are oxidase negative.

Think **COFFeE**:

Capsular

**O** antigen

Flagellar antigen

Ferment glucose

Enterobacteriaceae

***Klebsiella***

Pneumonia in alcoholics and diabetics. Red currant jelly sputum. Also cause of nosocomial UTIs.

**3 A's**:

Aspiration pneumonia

Abscess in lungs

Alcoholics

**Lactose-fermenting enteric bacteria**

These bacteria grow pink colonies on MacConkey's agar. Examples include *Klebsiella*, *E. coli*, *Enterobacter*, and *Citrobacter*.

Lactose is **KEE**.

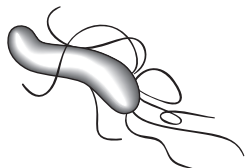
***Salmonella* vs. *Shigella***

Both are non-lactose fermenters; both invade intestinal mucosa and can cause bloody diarrhea. Only *SalMONella* is **M**otile and can invade further and disseminate hematogenously. Symptoms of salmonellosis may be prolonged with antibiotic treatments, and there is typically a monocyte response. *Shigella* is more virulent ( $10^1$  organisms) than *Salmonella* ( $10^5$  organisms).

Salmon swim (motile and disseminate). *Salmonella* has an animal reservoir; *Shigella* does not and is transmitted via “**F**ood, **F**ingers, **F**eces, and **F**lies.”

<b><i>Yersinia enterocolitica</i></b>	Usually transmitted from pet feces (e.g., puppies), contaminated milk, or pork. Outbreaks are common in day-care centers. Can mimic Crohn's or appendicitis.	
<b>Bugs causing food poisoning</b>	<p><i>Vibrio parahaemolyticus</i> and <i>V. vulnificus</i> in contaminated seafood.</p> <p><i>Bacillus cereus</i> in reheated rice.</p> <p><i>S. aureus</i> in meats, mayonnaise, custard.</p> <p><i>Clostridium perfringens</i> in reheated meat dishes.</p> <p><i>C. botulinum</i> in improperly canned foods (bulging cans).</p> <p><i>E. coli</i> O157:H7 in undercooked meat.</p> <p><i>Salmonella</i> in poultry, meat, and eggs.</p>	<p><i>S. aureus</i> food poisoning starts quickly and ends quickly.</p> <p>"Food poisoning from reheated rice? <b>Be serious!</b>" (<i>B. cereus</i>).</p>
<b>Bugs causing diarrhea</b>		
Type	Species	Findings
Bloody diarrhea	<i>Campylobacter</i>	Comma- or S-shaped organisms; growth at 42°C; oxidase positive
	<i>Salmonella</i>	Motile; lactose negative
	<i>Shigella</i>	Nonmotile; lactose negative; very low ID <sub>50</sub> ; causes dysentery
	Enterohemorrhagic <i>E. coli</i>	Shiga-like toxin; can cause HUS
	Enteroinvasive <i>E. coli</i>	O157:H7; invades colonic mucosa
Watery diarrhea	<i>Yersinia enterocolitica</i>	Day-care outbreaks, pseudoappendicitis
	<i>C. difficile</i>	Pseudomembranous colitis
	<i>Entamoeba histolytica</i>	Protozoan
	Enterotoxigenic <i>E. coli</i>	Traveler's diarrhea; no preformed toxin
	<i>Vibrio cholerae</i>	Comma-shaped organisms; rice-water diarrhea.
	<i>C. perfringens</i>	Also causes gas gangrene
	Protozoa	<i>Giardia</i> , <i>Cryptosporidium</i> (in immunocompromised)
	Viruses	Rotavirus, adenovirus, Norwalk virus
<b>cAMP inducers</b>	<ol style="list-style-type: none"> <li>1. <i>Vibrio cholerae</i> toxin permanently activates G<sub>s</sub>, causing rice-water diarrhea.</li> <li>2. Pertussis toxin permanently disables G<sub>i</sub>, causing whooping cough.</li> <li>3. <i>E. coli</i>—heat labile toxin. First three toxins act via ADP ribosylation that permanently activates adenylyl cyclase (↑ cAMP).</li> <li>4. <i>Bacillus anthracis</i> toxin is composed of an edema factor, a bacterial adenylyl cyclase (↑ cAMP).</li> </ol>	
	<p>Cholera turns the "on" on.</p> <p>Pertussis turns the "off" off.</p> <p>Pertussis toxin also promotes lymphocytosis by inhibiting chemokine receptors.</p>	

► MICROBIOLOGY—BACTERIOLOGY (*continued*)

<b>Legionella pneumophila</b>	Legionnaires' disease. Gram-negative rod. Gram stains poorly—use silver stain. Grow on charcoal yeast extract culture with iron and cysteine. Aerosol transmission from environmental water source habitat. No person-to-person transmission. Treat with erythromycin.	Think of a French legionnaire (soldier) with his silver helmet, sitting around a campfire (charcoal) with his iron dagger—he is no <b>sissy</b> ( <b>cysteine</b> ).	
<b>Pseudomonas aeruginosa</b>	<b>PSEUDO</b> <i>monas</i> is associated with wound and burn infections, <b>P</b> neumonia (especially in cystic fibrosis), <b>S</b> epsis (black lesions on skin), <b>E</b> xternal otitis (swimmer's ear), <b>U</b> TI, <b>D</b> rug use and <b>D</b> iabetic <b>O</b> steomyelitis, and hot tub folliculitis. Aerobic gram-negative rod. Non-lactose fermenting, oxidase positive. Produces pyocyanin (blue-green) pigment. Water source. Produces endotoxin (fever, shock) and exotoxin A (inactivates EF-2). Treat with aminoglycoside plus extended-spectrum penicillin (e.g., piperacillin, ticarcillin).	<b>AER</b> uginosa— <b>AER</b> obic. Think water connection and blue-green pigment. Think <i>Pseudomonas</i> in burn victims.	
<b>Helicobacter pylori</b> 	Causes gastritis and up to 90% of duodenal ulcers. Risk factor for peptic ulcer and gastric carcinoma. Gram-negative rod. Urease positive (e.g., urease breath test). Creates alkaline environment. Treat with triple therapy: (1) bismuth (Pepto-Bismol), metronidazole, and either tetracycline or amoxicillin; or (2) (more costly) metronidazole, omeprazole, and clarithromycin.	Pylori—think pylorus of stomach. <i>Proteus</i> and <i>H. pylori</i> are both urease positive (cleave urea to ammonia).	
<b>Zoonotic bacteria</b>			
Species	Disease	Transmission and source	
<i>Borrelia burgdorferi</i>	Lyme disease	Tick bite; <i>Ixodes</i> ticks that live on deer and mice	<b>Bugs From Your Pet</b> Undulate and
<i>Brucella</i> spp.	Brucellosis/ Undulant fever	Dairy products, contact with animals	Unpasteurized dairy products give you Undulant fever.
<i>Francisella tularensis</i>	Tularemia	Tick bite; rabbits, deer	
<i>Yersinia pestis</i>	Plague	Flea bite; rodents, especially prairie dogs	
<i>Pasteurella multocida</i>	Cellulitis	Animal bite; cats, dogs	
<b>Gardnerella vaginalis</b>	A pleomorphic, gram-variable rod that causes vaginosis—greenish vaginal discharge with fishy smell; nonpainful. <i>Mobiluncus</i> , an anaerobe, is also involved. Treat with metronidazole. Clue cells, or vaginal epithelial cells covered with bacteria, are visible under the microscope.		

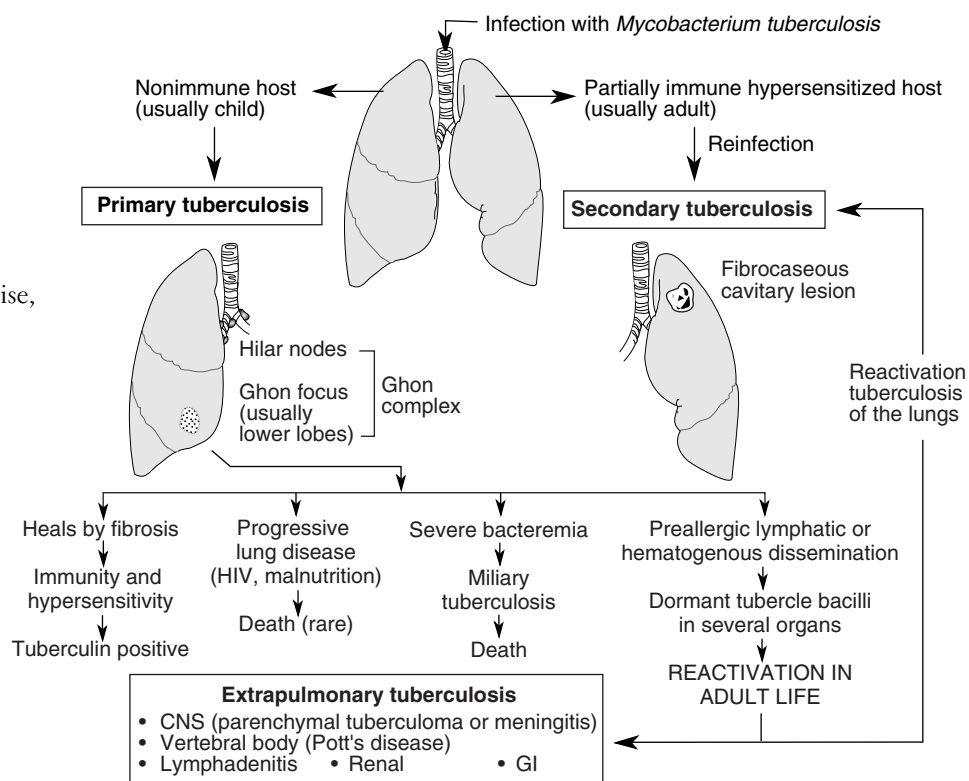
## 1° and 2° tuberculosis

### PPD+ :

Current infection  
Past exposure  
BCG vaccinated

### PPD- :

No infection  
Anergy (steroids,  
immunocompromise,  
malnutrition)



(Adapted, with permission, from Chandrasoma P, Taylor CR. *Concise Pathology*, 3rd ed. Stamford, CT: Appleton & Lange, 1998:523.)

### Ghon complex

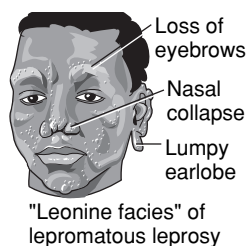
TB granulomas (Ghon focus) with lobar and perihilar lymph node involvement. Reflects 1° infection or exposure.

### Mycobacteria

*Mycobacterium tuberculosis* (TB, often resistant to multiple drugs).  
*M. kansasii* (pulmonary TB-like symptoms).  
*M. scrofulaceum* (cervical lymphadenitis in kids).  
*M. avium-intracellulare* (often resistant to multiple drugs; causes disseminated disease in AIDS).  
 All mycobacteria are acid-fast organisms.

TB symptoms include fever, night sweats, weight loss, and hemoptysis (see Color Image 2).


### Leprosy (Hansen's disease)



Caused by *Mycobacterium leprae*, an acid-fast bacillus that likes cool temperatures (infects skin and superficial nerves) and cannot be grown in vitro. Reservoir in United States: armadillos.  
 Treatment: long-term oral dapsone; toxicity is hemolysis and methemoglobinemia.  
 Alternate treatments include rifampin and combination of clofazimine and dapsone.

Hansen's disease has 2 forms: lepromatous and tuberculoid; lepromatous is worse (failed cell-mediated immunity); tuberculoid is self-limited.  
**LE**promatous = **LE**thal.

## ► MICROBIOLOGY—BACTERIOLOGY (continued)

<b>Rickettsiae</b>	<p>Rickettsiae are obligate intracellular parasites and need CoA and NAD. All except <i>Coxiella</i> are transmitted by an arthropod vector and cause headache, fever, and rash; <i>Coxiella</i> is an atypical rickettsia because it is transmitted by aerosol and causes pneumonia.</p> <p>Tetracycline is the treatment of choice for most rickettsial infections.</p>	Classic triad—headache, fever, rash (vasculitis).
<b>Rickettsial diseases and vectors</b>	<p>Rocky Mountain spotted fever (tick)—<i>Rickettsia rickettsii</i>.</p> <p>Endemic typhus (fleas)—<i>R. typhi</i>.</p> <p>Epidemic typhus (human body louse)—<i>R. prowazekii</i>.</p> <p>Q fever (inhaled aerosols)—<i>Coxiella burnetii</i>.</p> <p>Treatment for all: tetracycline.</p>	<p>TyPHus has centriPHugal (outward) spread of rash; sPotted fever is centriPetal (inward). Q fever is Q<sub>ueer</sub> because it has no rash, has no vector, and has negative Weil-Felix, and its causative organism can survive outside for a long time and does not have <i>Rickettsia</i> as its genus name.</p>
<b>Rocky Mountain spotted fever</b>	<p>Caused by <i>Rickettsia rickettsii</i>.</p> <p>Symptoms: rash on palms and soles (migrating to wrists, ankles, then trunk), headache, fever.</p> <p>Endemic to East Coast (in spite of name).</p>	Palm and sole rash is seen in Rocky Mountain spotted fever, syphilis, and coxsackievirus A infection (hand, foot, and mouth disease).
<b>Weil-Felix reaction</b>	Weil-Felix reaction assays for antirickettsial antibodies, which cross-react with <i>Proteus</i> antigen. Weil-Felix is usually positive for typhus and Rocky Mountain spotted fever but negative for Q fever.	
<b><i>Mycoplasma pneumoniae</i></b> 	<p>Classic cause of atypical “walking” pneumonia (insidious onset, headache, nonproductive cough, diffuse interstitial infiltrate). X-ray looks worse than patient. High titer of cold agglutinins (IgM). Grown on Eaton’s agar.</p> <p>Treatment: tetracycline or erythromycin (bugs are penicillin resistant because they have no cell wall).</p>	<p>No cell wall.</p> <p>Only bacterial membrane containing cholesterol.</p> <p><i>Mycoplasma pneumoniae</i> is more common in patients &lt; 30 years of age.</p> <p>Frequent outbreaks in military recruits and prisons.</p>

**Chlamydiae**

Chlamydiae are obligate intracellular parasites that cause mucosal infections. 2 forms:

1. Elementary body (small, dense), which Enters cell via endocytosis
2. Initial or Reticulate body, which Replicates in cell by fission

*Chlamydia trachomatis* causes reactive arthritis, conjunctivitis, and nongonococcal urethritis.

*C. pneumoniae* and *C. psittaci* cause atypical pneumonia; transmitted by aerosol.

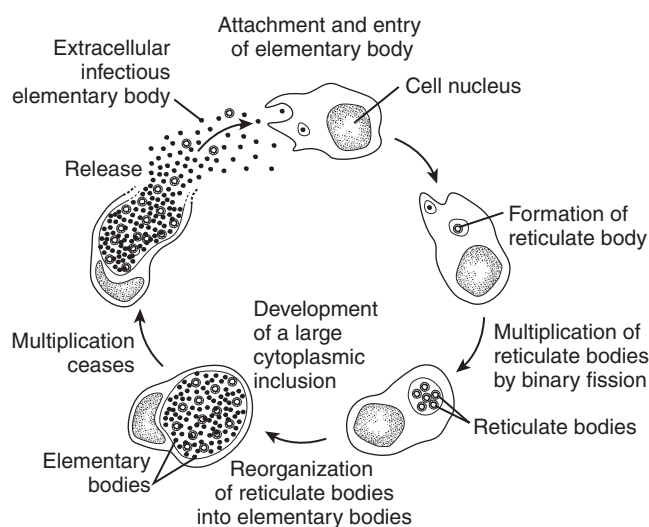
Treatment: erythromycin or tetracycline.

*Chlamys* = cloak (intracellular).

*Chlamydia psittaci*—notable for an avian reservoir.

The chlamydial peptidoglycan wall is unusual in that it lacks muramic acid.

Lab diagnosis: cytoplasmic inclusions seen on Giemsa or fluorescent antibody-stained smear.

***Chlamydia trachomatis* serotypes**

Types A, B, and C—chronic infection, cause blindness in Africa.

Types D–K—urethritis/PID, ectopic pregnancy, neonatal pneumonia, or neonatal conjunctivitis.

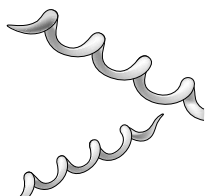
Types L1, L2, and L3—lymphogranuloma venereum (acute lymphadenitis—positive Frei test).

ABC = Africa/Blindness/Chronic infection.

L1–3 = Lymphogranuloma venereum.

D–K = everything else.

Neonatal disease acquired by passage through infected birth canal. Treat with erythromycin eye drops.

**Spirochetes**

The spirochetes are spiral-shaped bacteria with axial filaments and include *Borrelia* (big size), *Leptospira*, and *Treponema*. Only *Borrelia* can be visualized using aniline dyes (Wright's or Giemsa stain) in light microscopy. *Treponema* is visualized by dark-field microscopy.

BLT. B is Big.

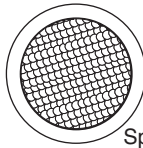

## ► MICROBIOLOGY–MYCOLOGY

<b>Lyme disease</b>	<p>Caused by <i>Borrelia burgdorferi</i>, which is transmitted by the tick <i>Ixodes</i>.</p> <p>Classic symptom is erythema chronicum migrans, an expanding “bull’s eye” red rash with central clearing. Also affects joints, CNS, and heart.</p> <p>Mice are important reservoirs. Deer required for tick life cycle.</p> <p>Treat with tetracycline.</p> <p>Named after Lyme, Connecticut; disease is common in northeastern United States.</p> <p>Transmission is most common in summer months.</p>	<p>3 stages of Lyme disease:</p> <p>Stage 1—erythema chronicum migrans, flulike symptoms.</p> <p>Stage 2—neurologic and cardiac manifestations.</p> <p>Stage 3—autoimmune migratory polyarthritis.</p> <p><b>BAKE</b> a Key <b>Lyme</b> pie:  <b>B</b>ell’s palsy, <b>A</b>rthritis, <b>K</b>ardiac block, <b>E</b>rythema chronicum migrans.</p>												
<b>Treponemal disease</b>	<p>Treponemes are spirochetes.</p> <p><i>Treponema pallidum</i> causes syphilis.</p> <p><i>T. pertenue</i> causes yaws (a tropical infection that is not an STD, although VDRL test is positive).</p>													
<b>Syphilis</b>	Caused by spirochete <i>Treponema pallidum</i> .	Treat with penicillin G.												
1° syphilis	Presents with painless chancre (localized disease).													
2° syphilis	Disseminated disease with constitutional symptoms, maculopapular rash (palms and soles), condylomata lata.	Secondary syphilis = Systemic.												
3° syphilis	Gummas, aortitis, neurosyphilis (tabes dorsalis), Argyll Robertson pupil (see Color Image 12).	Signs: broad-based ataxia, positive Romberg, Charcot joints, stroke without hypertension.												
Congenital syphilis	Saber shins, saddle nose, deafness.													
<b>Argyll Robertson pupil</b>	Argyll Robertson pupil constricts with accommodation but is not reactive to light. Pathognomonic for 3° syphilis.	“Prostitute’s pupil”—accommodates but does not react.												
<b>VDRL vs. FTA-ABS</b>	<p>FTA-ABS is specific for treponemes, turns positive earliest in disease, and remains positive longest.</p> <table> <tr> <th>VDRL</th><th>FTA</th><th>Interpretation</th></tr> <tr> <td>+</td><td>+</td><td>Active infection</td></tr> <tr> <td>+</td><td>–</td><td>Probably false positive</td></tr> <tr> <td>–</td><td>+</td><td>Successfully treated</td></tr> </table>	VDRL	FTA	Interpretation	+	+	Active infection	+	–	Probably false positive	–	+	Successfully treated	<p><b>FTA-ABS = Find The Antibody-ABSolutely:</b></p> <ol style="list-style-type: none"> <li>Most specific</li> <li>Earliest positive</li> <li>Remains positive the longest</li> </ol>
VDRL	FTA	Interpretation												
+	+	Active infection												
+	–	Probably false positive												
–	+	Successfully treated												
<b>VDRL false positives</b>	VDRL detects nonspecific antibody that reacts with beef cardiolipin. Used for diagnosis of syphilis, but many biologic false positives, including viral infection (mononucleosis, hepatitis), some drugs, rheumatic fever, rheumatoid arthritis, SLE, and leprosy.	<p><b>VDRL:</b></p> <p>Viruses (mono, hepatitis)</p> <p>Drugs</p> <p>Rheumatic fever and rheumatic arthritis</p> <p>Lupus and leprosy</p>												



<b>Spores: fungal</b>	Most fungal spores are asexual. Both coccidioidomycosis and histoplasmosis are transmitted by inhalation of asexual spores.	Conidia—aseexual fungal spores (e.g., blastoconidia, arthroconidia).
<b><i>Candida albicans</i></b>	Systemic or superficial fungal infection (budding yeast with pseudohyphae in culture at 20°C; germ tube formation at 37°C). Thrush esophagitis with immunocompromised patients (neonates, steroids, diabetes, AIDS), endocarditis in IV drug users, vaginitis (post-antibiotic), diaper rash. Treatment: nystatin for superficial infection; amphotericin B for serious systemic infection.	<i>Alba</i> = white.

### Systemic mycoses

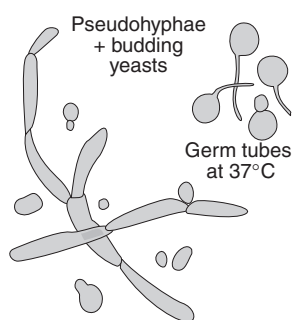
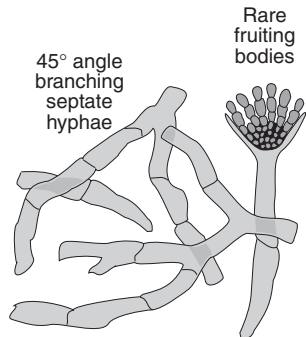
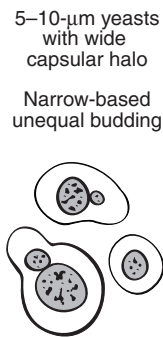
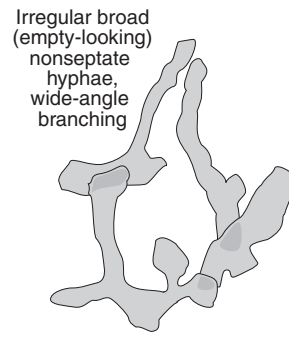
Disease	Endemic location	Notes
Coccidioidomycosis	Southwestern United States, California.	San Joaquin Valley or desert (desert bumps) “valley fever” (see Color Image 7)
 Spherule filled with endospores		
Histoplasmosis	Mississippi and Ohio river valleys.	Bird or bat droppings; intracellular (tiny yeast inside macrophages)
Paracoccidioidomycosis	Rural Latin America.	“Captain’s wheel” appearance
Blastomycosis	States east of Mississippi River and Central America.	Big, Broad-Based Budding
 Broad-based budding	All of the above are caused by <b>dimorphic</b> fungi, which are mold in soil (at lower temperature) and yeast in tissue (at higher/body temperature: 37°C) except coccidioidomycosis, which is a spherule in tissue. Treat with fluconazole or ketoconazole for local infection; amphotericin B for systemic infection. Systemic mycoses can mimic TB (granuloma formation).	<b>Cold = Mold</b> <b>Heat = Yeast</b> Culture on Sabouraud’s agar

### Cutaneous mycoses

Tinea versicolor	Caused by <i>Malassezia furfur</i> . Causes hypopigmented skin lesions. Occurs in hot, humid weather. Treat with topical miconazole, selenium sulfide (Selsun).
Tinea nigra	Caused by <i>Cladosporium werneckii</i> . Infection of keratinized layer of skin. Appears as brownish spot. Treat with topical salicylic acid.
Tinea pedis, tinea cruris, tinea corporis, tinea capitis	Pruritic lesions with central clearing resembling a ring, caused by dermatophytes ( <i>Microsporum</i> , <i>Trichophyton</i> , and <i>Epidermophyton</i> ). See mold hyphae in KOH prep, not dimorphic. Pets are a reservoir for <i>Microsporum</i> and can be treated with topical azoles.

► MICROBIOLOGY–MYCOLOGY (*continued*)**Opportunistic fungal infections**

<i>Candida albicans</i>	Thrush in immunocompromised (neonates, steroids, diabetes, AIDS), vulvovaginitis (high pH, diabetes, use of antibiotics), disseminated candidiasis (to any organ), chronic mucocutaneous candidiasis (see Color Image 9).
<i>Aspergillus fumigatus</i>	Allergic bronchopulmonary aspergillosis, lung cavity aspergilloma (“fungus ball”), invasive aspergillosis. <b>Mold</b> with septate hyphae that branch at a V-shaped (45°) angle. Not dimorphic.
<i>Cryptococcus neoformans</i>	Cryptococcal meningitis, cryptococcosis. Heavily encapsulated <b>yeast</b> . Not dimorphic. Found in soil, pigeon droppings. Culture on Sabouraud’s agar. Stains with India ink. Latex agglutination test detects polysaccharide capsular antigen (see Color Image 8).
<i>Mucor</i> and <i>Rhizopus</i> spp.	Mucormycosis. <b>Mold</b> with irregular nonseptate hyphae branching at wide angles ( $\geq 90^\circ$ ). Disease mostly in ketoacidotic diabetic and leukemic patients. Fungi also proliferate in the walls of blood vessels and cause infarction of distal tissue. Rhinocerebral, frontal lobe abscesses.

**Candida****Aspergillus****Cryptococcus****Mucor*****Pneumocystis carinii***

Causes diffuse interstitial pneumonia (PCP). Yeast (originally classified as protozoan). Inhaled. Most infections asymptomatic. Immunosuppression (e.g., AIDS) predisposes to disease. Diagnosed by lung biopsy or lavage. Identified by methenamine silver stain of lung tissue. Treat with TMP-SMX, pentamidine, dapsone. Start prophylaxis when CD4 drops < 200 cells/mL in HIV patients (see Color Image 17).

***Sporothrix schenckii***

Sporotrichosis. Dimorphic fungus that lives on vegetation. When traumatically introduced into the skin, typically by a thorn (“rose gardener’s” disease), causes local pustule or ulcer with nodules along draining lymphatics (ascending lymphangitis). Little systemic illness. Cigar-shaped budding yeast visible in pus. Treat with itraconazole or potassium iodide.

**Medically important protozoa**

Organism	Disease	Transmission	Diagnosis	Treatment
<i>Entamoeba histolytica</i>	Amebiasis: bloody diarrhea, (dysentery), liver abscess, RUQ pain	Cysts in water	Serology and/or trophozoites or cysts in stool	Metronidazole and iodoquinol
<i>Giardia lamblia</i> (see Color Image 5)	Giardiasis: bloating, flatulence, foul-smelling diarrhea (often seen in campers/hikers)	Cysts in water	Trophozoites or cysts in stool	Metronidazole
<i>Cryptosporidium</i>	Severe diarrhea in AIDS Mild disease (watery diarrhea) in non-HIV	Cysts in water	Cysts on acid-fast stain	None
<i>Toxoplasma</i>	Brain abscess in HIV, birth defects (ring-enhancing brain lesions)	Cysts in meat or cat feces	Serology, biopsy	Sulfadiazine + pyrimethamine
<i>Plasmodium</i> <i>P. vivax</i> <i>P. ovale</i> <i>P. malariae</i> <i>P. falciparum</i>	Malaria: cyclic fever, headache, anemia, splenomegaly Malaria—severe (cerebral) with <i>P. falciparum</i>	Mosquito ( <i>Anopheles</i> )	Blood smear	Chloroquine (primaquine to prevent relapse caused by <i>P. vivax</i> , <i>P. ovale</i> ), sulfadoxine + pyrimethamine, mefloquine, quinine
<i>Trichomonas vaginalis</i> (see Color Image 10)	Vaginitis: foul-smelling, greenish discharge; itching and burning	Sexual	Trophozoites (motile) on wet mount	Metronidazole
<i>Trypanosoma cruzi</i>	Chagas' disease (dilated cardiomyopathy, megacolon, megaesophagus)	Reduviid bug	Blood smear	Nifurtimox
<i>Trypanosoma</i> <i>T. gambiense</i> <i>T. rhodesiense</i>	African sleeping sickness	Tsetse fly	Blood smear	Suramin for blood-borne disease or melarsoprol for CNS penetration
<i>Leishmania donovani</i>	Visceral leishmaniasis (kala-azar)	Sandfly	Macrophages containing amastigotes	Sodium stibogluconate
<i>Babesia</i>	Babesiosis: fever and anemia	<i>Ixodes</i> tick	Blood smear, no RBC pigment, appears as "maltese cross"	Quinine, clindamycin
<i>Naegleria</i>	Rapidly fatal meningoencephalitis	Swimming in freshwater lakes (enter via cribriform plate)	Amebas in spinal fluid	None

## ► MICROBIOLOGY–PARASITOLOGY (continued)

**Medically important helminths**

Organism	Transmission/disease	Treatment
<b>Cestodes (tapeworms)</b>		
<i>Taenia solium</i>	Undercooked pork tapeworm; larvae cause mass lesions in the brain, cysticercosis.	Praziquantel/niclosamide; albendazole for cysticercosis
<i>Echinococcus granulosus</i>	Eggs in dog feces when ingested can cause cysts in liver; causes anaphylaxis if echinococcal antigens are released from cysts.	Albendazole
<b>Trematodes (flukes)</b>		
<i>Schistosoma</i>	Snails are host; cercariae penetrate skin of humans; causes granulomas, fibrosis, and inflammation of the spleen and liver.	Praziquantel
<i>Clonorchis sinensis</i>	Undercooked fish; causes inflammation of the biliary tract.	Praziquantel
<i>Paragonimus westermani</i>	Undercooked crab meat; causes inflammation and 2° bacterial infection of the lung.	Praziquantel
<b>Nematodes (roundworms)</b>		
<i>Ancylostoma duodenale</i> (hookworm)	Larvae penetrate skin of feet; intestinal infection can cause anemia.	Mebendazole/pyrantel pamoate
<i>Ascaris lumbricoides</i> (giant roundworm)	Eggs are visible in feces; intestinal infection.	Mebendazole/pyrantel pamoate
<i>Enterobius vermicularis</i> (pinworm)	Food contaminated with eggs; intestinal infection; causes anal pruritus (the Scotch tape test).	Mebendazole/pyrantel pamoate
<i>Strongyloides stercoralis</i>	Larvae in soil penetrate the skin; intestinal infection.	Ivermectin/thiabendazole
<i>Trichinella spiralis</i>	Undercooked meat, usually pork; inflammation of muscle, periorbital edema.	Thiabendazole
<i>Dracunculus medinensis</i>	In drinking water; skin inflammation and ulceration.	Niridazole
<i>Loa loa</i>	Transmitted by deer fly; causes swelling in skin (can see worm crawling in conjunctiva).	Diethylcarbamazine
<i>Onchocerca volvulus</i>	Transmitted by female blackflies; causes river blindness.	Ivermectin
<i>Toxocara canis</i>	Food contaminated with eggs; causes granulomas (if in retina → blindness) and visceral larva migrans.	Diethylcarbamazine
<i>Wuchereria bancrofti</i>	Female mosquito; causes blockage of lymphatic vessels (elephantiasis).	Diethylcarbamazine

Parasite hints	Findings	Organism
	Brain cysts, seizures	<i>Taenia solium</i> (cysticercosis)
	Liver cysts	<i>Echinococcus granulosus</i>
	B <sub>12</sub> deficiency	<i>Diphyllobothrium latum</i>
	Biliary tract disease	<i>Clonorchis sinensis</i>
	Hemoptysis	<i>Paragonimus westermani</i>
	Portal hypertension	<i>Schistosoma mansoni</i>
	Hematuria, bladder cancer	<i>Schistosoma haematobium</i>
	Microcytic anemia	<i>Ancylostoma</i> , <i>Necator</i>
	Perianal pruritus	<i>Enterobius</i>

<b>“Tricky T’s”</b>	<p><i>Chlamydia trachomatis</i>—bacteria, STD.</p> <p><i>Trichomonas vaginalis</i>—protozoan, STD.</p> <p><i>Trichinella spiralis</i>—worm in undercooked meat.</p> <p><i>Trypanosoma</i>—causes Chagas’ disease (<i>T. cruzi</i>) or African sleeping sickness.</p> <p><i>Treponema</i>—spirochete; causes syphilis (<i>T. pallidum</i>) or yaws (<i>T. pertenue</i>).</p>
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### ► MICROBIOLOGY—VIROLOGY

<b>DNA viral genomes</b>	All DNA viruses except the Parvoviridae are dsDNA. All are linear except papovaviruses and hepadnaviruses (circular).	All are dsDNA (like our cells), except “ <b>part-of-a-virus</b> ” ( <b>parvovirus</b> ) is ssDNA.
<b>RNA viral genomes</b>	All RNA viruses except Reoviridae are ssRNA.	All are ssRNA (like our mRNA), except “ <b>repeato-virus</b> ” ( <b>reovirus</b> ) is dsRNA.
<b>Naked viral genome infectivity</b>	<p>Naked nucleic acids of most dsDNA (except poxviruses and HBV) and (+) strand ssRNA (<math>\approx</math> mRNA) viruses are infectious. Naked nucleic acids of (–) strand ssRNA and dsRNA viruses are not infectious.</p> <p><b>Naked</b> (nonenveloped) RNA viruses include Calicivirus, Picornavirus, and Reovirus.</p>	<p>Viral nucleic acids with the same structure as host nucleic acids are infective alone; others require special enzymes (contained in intact virion).</p> <p><b>Naked CPR.</b></p>
<b>Enveloped viruses</b>	Generally, enveloped viruses acquire their envelopes from plasma membrane when they exit from cell. Exceptions are herpesviruses, which acquire envelopes from nuclear membrane.	
<b>Virus ploidy</b>	All viruses are haploid (with 1 copy of DNA or RNA) except retroviruses, which have 2 identical ssRNA molecules ( $\approx$ diploid).	
<b>Viral replication</b>		
DNA viruses	All replicate in the nucleus (except poxvirus).	
RNA viruses	All replicate in the cytoplasm (except influenza virus and retroviruses).	

► MICROBIOLOGY–VIROLOGY (*continued*)**DNA virus characteristics**

Some general rules—all DNA viruses:

1. Are **HHAPPPy** viruses
2. Are double stranded
3. Are linear
4. Are icosahedral
5. Replicate in the nucleus

Naked DNA viruses are **PAP** = Parvo, Adeno, Papova; enveloped DNA viruses are **HPH** = Hepadna, Pox, Herpes.

Hepadna, Herpes, Adeno, Pox, Parvo, Papova.  
**EXCEPT Parvo** (single stranded).  
**EXCEPT Papovavirus** (circular, supercoiled) and **Hepadna** (circular, incomplete).  
**EXCEPT Pox** (complex).  
**EXCEPT Pox** (carries own DNA-dependent RNA polymerase).  
 You need to be **naked** for a **PAP** smear.

**DNA viruses**

Viral Family	Envelope	DNA Structure	Medical Importance
Hepadnavirus	Yes	DS – partial circular	HBV Acute or chronic hepatitis Vaccine available—use has increased tremendously Not a retrovirus but has reverse transcriptase
Herpesviruses	Yes	DS – linear	HSV-1—oral (and some genital) lesions, keratoconjunctivitis HSV-2—genital (and some oral) lesions VZV—chickenpox, zoster, shingles EBV—mononucleosis, Burkitt's lymphoma CMV—infection in immunosuppressed patients, especially transplant recipients; congenital defects HHV-6—roseola (exanthem subitum) HHV-8—Kaposi's sarcoma—associated herpesvirus (KSHV)
Adenovirus	No	DS – linear	Febrile pharyngitis—sore throat Pneumonia Conjunctivitis—“pink eye”
Parvovirus	No	SS – linear (–) (smallest DNA virus)	B19 virus—aplastic crises in sickle cell disease, “slapped cheeks” rash—erythema infectiosum (fifth disease), hydrops fetalis
Papovavirus	No	DS – circular	HPV—warts, CIN, cervical cancer JC—progressive multifocal leukoencephalopathy (PML) in HIV
Poxvirus	Yes	DS – linear (largest DNA virus)	Smallpox, although eradicated, could be used in germ warfare Vaccinia—cowpox (“milkmaid's blisters”) Molluscum contagiosum

**RNA viruses**

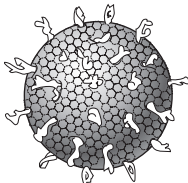
Viral Family	Envelope	RNA Structure	Capsid Symmetry	Medical Importance
Picornaviruses	No	SS + linear	Icosahedral	Poliovirus—polio-Salk/Sabin vaccines—IPV/OPV Echovirus—aseptic meningitis Rhinovirus—“common cold” Coxsackievirus—aseptic meningitis herpangina—febrile pharyngitis hand, foot, and mouth disease myocarditis HAV—acute viral hepatitis
Caliciviruses	No	SS + linear	Icosahedral	HEV Norwalk virus—viral gastroenteritis
Reoviruses	No	DS linear Segmented	Icosahedral (double)	Reovirus—Colorado tick fever Rotavirus—#1 cause of fatal diarrhea in children
Flaviviruses	Yes	SS + linear	Icosahedral	HCV Yellow fever Dengue St. Louis encephalitis West Nile virus
Togaviruses	Yes	SS + linear	Icosahedral	Rubella (German measles) Eastern equine encephalitis Western equine encephalitis
Retroviruses	Yes	SS + linear	Icosahedral	Have reverse transcriptase HIV—AIDS HTLV—T-cell leukemia
Coronaviruses	Yes	SS + linear	Helical	Coronavirus—“common cold” and SARS
Orthomyxoviruses	Yes	SS – linear Segmented	Helical	Influenza virus
Paramyxoviruses	Yes	SS – linear Nonsegmented	Helical	<b>PaRaMyxovirus:</b> Parainfluenza—croup RSV—bronchiolitis in babies; Rx—ribavirin Measles Mumps
Rhabdoviruses	Yes	SS – linear	Helical	Rabies
Filoviruses	Yes	SS – linear	Helical	Ebola/Marburg hemorrhagic fever—often fatal!
Arenaviruses	Yes	SS – circular	Helical	LCV—lymphocytic choriomeningitis Meningitis—spread by mice
Bunyaviruses	Yes	SS – circular	Helical	California encephalitis Sandfly/Rift Valley fevers Crimean-Congo hemorrhagic fever Hantavirus—hemorrhagic fever, pneumonia
Deltavirus	Yes	SS – circular	Helical	HDV
SS, single-stranded; DS, double-stranded; +, + polarity; –, – polarity				

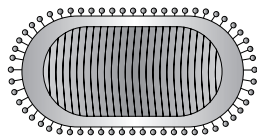
(Adapted, with permission, from Levinson W, Jawetz E. *Medical Microbiology and Immunology: Examination and Board Review*, 6th ed. New York: McGraw-Hill, 2000:182.)

► MICROBIOLOGY–VIROLOGY (*continued*)

<b>Viral vaccines</b>		
	Live attenuated vaccines induce humoral and cell-mediated immunity but have reverted to virulence on rare occasions. Killed vaccines induce only humoral immunity but are stable.	Dangerous to give live vaccines to immunocompromised patients or their close contacts.
	Live attenuated—measles, mumps, rubella, Sabin polio, VZV, yellow fever, smallpox, adenovirus.	MMR = measles, mumps, rubella.
	Killed—rabies, influenza, Salk polio, and HAV vaccines.	Salk = Killed.
	Egg-based—Flu, MMR, Yellow fever.	RIP Always
	Recombinant—HBV (antigen = recombinant HBsAg).	FRY an egg.
<b>Viral genetics</b>		
Recombination	Exchange of genes between 2 chromosomes by crossing over within regions of significant base sequence homology.	
Reassortment	When viruses with segmented genomes (e.g., influenza virus) exchange segments. High-frequency recombination. Cause of worldwide pandemics.	
Complementation	When 1 of 2 viruses that infect the cell has a mutation that results in a nonfunctional protein. The nonmutated virus “complements” the mutated one by making a functional protein that serves both viruses.	
Phenotypic mixing	Genome of virus A can be coated with the surface proteins of virus B. Type B protein coat determines the infectivity of the phenotypically mixed virus. However, the progeny from this infection has a type A coat and is encoded by its type A genetic material.	
<b>Viral pathogens</b>		
<b>Structure</b>	<b>Viruses</b>	
DNA enveloped viruses	Herpesviruses (HSV types 1 and 2, VZV, CMV, EBV), HBV, smallpox virus	
DNA nucleocapsid viruses	Adenovirus, papillomaviruses, parvovirus	
RNA enveloped viruses	Influenza virus, parainfluenza virus, RSV, measles virus, mumps virus, rubella virus, rabies virus, HTLV, HIV	
RNA nucleocapsid viruses	Enteroviruses (poliovirus, coxsackievirus, echovirus, HAV), rhinovirus, reovirus	
<b>Negative-stranded viruses</b>		
	Must transcribe negative strand to positive, using RNA polymerase. They include Arenaviruses, Bunyaviruses, Paramyxoviruses, Orthomyxoviruses, Filoviruses, and Rhabdoviruses.	Always Bring Polymerase or Fail Replication.
<b>Segmented viruses</b>		
	All are RNA viruses. They include Bunyaviruses, Orthomyxoviruses (influenza viruses), Arenaviruses, and Reoviruses. Influenza virus consists of 8 segments of negative-stranded RNA. These segments can undergo reassortment, causing antigenic shifts that lead to worldwide epidemics of the flu.	BOAR.



<b>Picornavirus</b>	Includes <b>Poliovirus</b> , <b>Echovirus</b> , <b>Rhinovirus</b> , <b>Coxsackievirus</b> , <b>HAV</b> . RNA is translated into 1 large polypeptide that is cleaved by proteases into functional viral proteins. Can cause aseptic (viral) meningitis (except rhinovirus and HAV).	Pico <b>RNA</b> virus = small <b>RNA</b> virus. <b>PERCH</b> on a “ <b>peak</b> ” (pico).
<b>Rhinovirus</b>	Nonenveloped RNA virus. Cause of common cold— > 100 serologic types.	<b>Rhino</b> has a runny nose.
<b>Rotavirus</b> 	Rotavirus, the most important global cause of infantile gastroenteritis, is a segmented dsRNA virus (a reovirus). Major cause of acute diarrhea in the United States during winter. Villous destruction with atrophy leads to decreased absorption of Na <sup>+</sup> and water.	<b>ROTA</b> = Right Out The Anus.
<b>Paramyxoviruses</b>	Paramyxoviruses include those that cause parainfluenza (croup), mumps, and measles as well as RSV, which causes respiratory tract infection (bronchiolitis, pneumonia) in infants. Paramyxoviruses cause disease in children. All paramyxoviruses have 1 serotype except parainfluenza virus, which has 4.	
<b>Mumps virus</b>	A paramyxovirus with 1 serotype. Symptoms: <b>Parotitis</b> , <b>Orchitis</b> (inflammation of testes), and aseptic <b>Meningitis</b> . Can cause sterility (especially after puberty).	Mumps makes your parotid glands and testes as big as <b>POM</b> -poms.
<b>Measles virus</b>	A paramyxovirus that causes measles. Koplik spots (bluish-gray spots on buccal mucosa) are diagnostic. SSPE, encephalitis (1:2000), and giant cell pneumonia (rarely, in immunosuppressed) are possible sequelae. Rash has head to toe spread.	<b>3 C's</b> of measles: Cough Coryza Conjunctivitis Also look for <b>Koplik</b> spots.
<b>Influenza viruses</b>	Enveloped, single-stranded RNA viruses with segmented genome. Contain hemagglutinin and neuraminidase antigens. Responsible for worldwide influenza epidemics; patients at risk for fatal bacterial superinfection. Rapid genetic changes.	Killed viral vaccine is major mode of protection; reformulated vaccine offered each fall to elderly, health-care workers, etc.
Genetic shift (pandemic)	Reassortment of viral genome (such as when human flu A virus recombines with swine flu A virus).	<b>Sudden Shift</b> is more deadly than gra <b>Dual</b> <b>Drift</b> .
Genetic drift (epidemic)	Minor changes based on random mutation.	
Treatment	Amantadine and rimantadine useful for influenza A (especially prophylaxis). Zanamivir and oseltamivir (neuraminidase inhibitors) useful for both influenza A and B.	

► MICROBIOLOGY—VIROLOGY (*continued*)**Rabies virus**

Negri bodies are characteristic cytoplasmic inclusions in neurons infected by rabies virus. Has bullet-shaped capsid. Rabies has long incubation period (weeks to 3 months). Causes fatal encephalitis with seizures and hydrophobia. More commonly from bat, raccoon, and skunk bites than from dog bites in the United States.

Travels to the CNS by migrating in a retrograde fashion up nerve axons.

**Arboviruses**

Transmitted by arthropods (mosquitoes, ticks). Classic examples are dengue fever (also known as break-bone fever) and yellow fever. A variant of dengue fever in Southeast Asia is hemorrhagic shock syndrome.

**ARBO**virus—**AR**thropod-**BO**rne virus, including flavivirus, togavirus, and bunyavirus. Fever Transmitted by **B**ites.

**Yellow fever**

Caused by flavivirus, an arbovirus transmitted by *Aedes* mosquitos. Virus has a monkey or human reservoir. Symptoms: high fever, black vomitus, and jaundice. Councilman bodies (acidophilic inclusions) may be seen in liver.

*Flavi* = yellow.

**Herpesviruses**

Virus	Diseases	Route of transmission	
HSV-1	Gingivostomatitis, keratoconjunctivitis, temporal lobe encephalitis, herpes labialis (see Color Image 11)	Respiratory secretions, saliva	Get herpes in a <b>CHEV</b> olet: <b>CMV</b>
HSV-2	Herpes genitalis, neonatal herpes	Sexual contact, perinatal	<b>HSV</b>
VZV	Varicella-zoster (shingles), encephalitis, pneumonia (see Color Image 15)	Respiratory secretions	<b>EBV</b>
EBV	Infectious mononucleosis, Burkitt's lymphoma	Respiratory secretions, saliva	<b>VZV</b>
CMV	Congenital infection, mononucleosis (negative Monospot), pneumonia	Congenital, transfusion, sexual contact, saliva, urine, transplant (see Color Image 6)	
HHV-8	Kaposi's sarcoma (HIV patients)	Sexual contact	

**Mononucleosis**

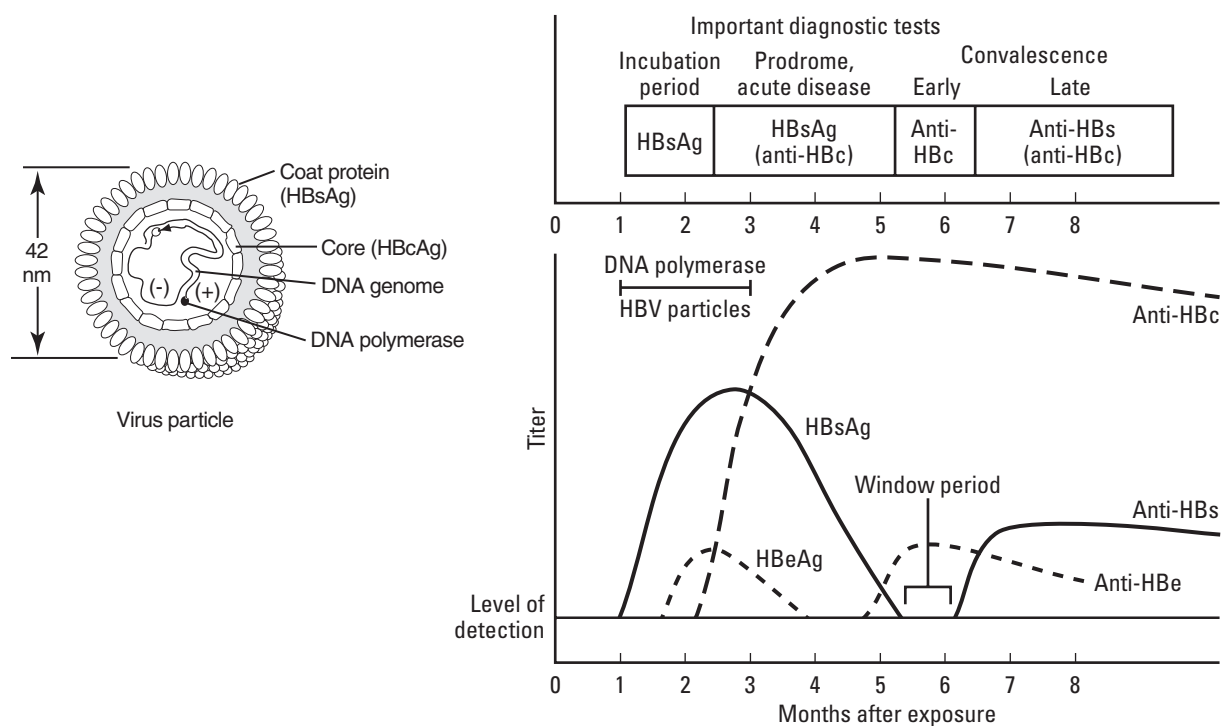
Caused by EBV, a herpesvirus. Infects B cells. Characterized by fever, hepatosplenomegaly, pharyngitis, and lymphadenopathy (especially posterior auricular nodes). Peak incidence 15–20 years old. Positive heterophil antibody test. Abnormal circulating cytotoxic T cells (atypical lymphocytes).

Most common during peak kissing years (“kissing disease”). Monospot test—heterophil antibodies detected by agglutination of sheep RBCs.

<b>Tzanck test</b>	A smear of an opened skin vesicle to detect multinucleated giant cells. Used to assay for HSV-1, HSV-2, and VZV.	<b>Tzanck</b> heavens I do not have herpes.
<b>Hepatitis transmission</b>	<p>HAV (RNA picornavirus) is transmitted primarily by fecal-oral route. Short incubation (3 weeks). No carriers.</p> <p>HBV (DNA hepadnavirus) is transmitted primarily by parenteral, sexual, and maternal-fetal routes. Long incubation (3 months). Carriers. Reverse transcription occurs; however, the virion enzyme is a DNA-dependent DNA polymerase.</p> <p>HCV (RNA flavivirus) is transmitted primarily via blood and resembles HBV in its course and severity. Carriers. Common cause of IV drug use hepatitis in the United States.</p> <p>HDV (delta agent) is a defective virus that requires HBsAg as its envelope. Carriers.</p> <p>HEV (RNA calicivirus) is transmitted enterically and causes water-borne epidemics. Resembles HAV in course, severity, incubation. High mortality rate in pregnant women.</p> <p>Both HBV and HCV predispose a patient to chronic active hepatitis, cirrhosis, and hepatocellular carcinoma.</p>	<p>Hep <b>A</b>: Asymptomatic (usually), <b>A</b>cute, <b>A</b>lone (no carriers; naked ssRNA).</p> <p>Hep <b>B</b>: Blood borne.</p> <p>Hep <b>C</b>: Chronic, Cirrhosis, Carcinoma, Carriers.</p> <p>Hep <b>D</b>: Defective, <b>D</b>ependent on HBV.</p> <p>Hep <b>E</b>: Enteric, <b>E</b>xpectant mothers, <b>E</b>pidemics.</p> <p>A and E by fecal-oral route: "The <b>vowels</b> hit your <b>bowels</b>."</p>

► MICROBIOLOGY–VIROLOGY (*continued*)**Hepatitis serologic markers**

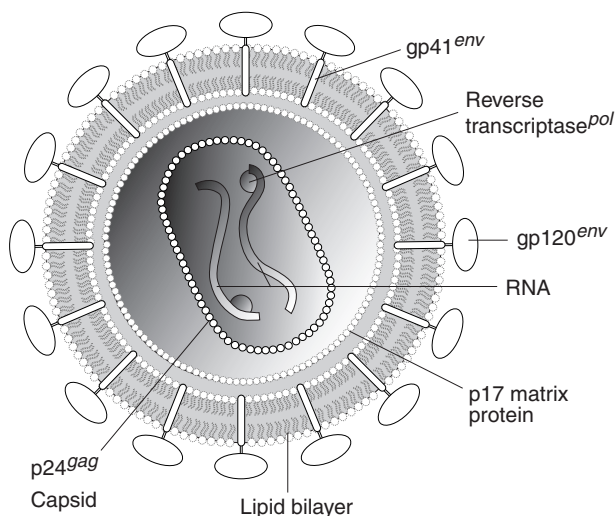
IgM HAVAb	IgM antibody to HAV; best test to detect active hepatitis A.
HBsAg	Antigen found on surface of HBV; continued presence indicates carrier state.
HBsAb	Antibody to HBsAg; <b>provides immunity</b> to hepatitis B.
HBcAg	Antigen associated with core of HBV.
HBcAb	Antibody to HBcAg; positive during <b>window period</b> . IgM HBcAb is an indicator of recent disease.
HBeAg	A second, different antigenic determinant in the HBV core. Important indicator of transmissibility. ( <b>BE</b> ware!)
HBeAb	Antibody to e antigen; indicates low transmissibility.



Test	Acute Disease	Window Phase	Complete Recovery	Chronic Carrier
HBsAg	+	–	–	+
HBsAb	–	–	+	– <sup>b</sup>
HBcAb	+ <sup>a</sup>	+	+	+

<sup>a</sup>IgM in acute stage; IgG in chronic or recovered stage.

<sup>b</sup>Patient has surface antibody but available antibody is bound to HBsAg.

**HIV**

(Adapted, with permission, from Levinson W. *Medical Microbiology and Immunology: Examination and Board Review*, 8th ed. New York: McGraw-Hill, 2004:314.)

Diploid genome (2 molecules of RNA).  
p24 = rectangular nucleocapsid protein.  
gp41 and gp120 = envelope proteins.

Reverse transcriptase synthesizes dsDNA from RNA; dsDNA integrates into host genome.

**HIV diagnosis**

Presumptive diagnosis made with ELISA (sensitive, high false-positive rate and low threshold, RULE OUT test); positive results are then confirmed with Western blot assay (specific, high false-negative rate and high threshold, RULE IN test).  
HIV PCR/viral load tests are increasing in popularity: they allow physician to monitor the effect of drug therapy on viral load.

ELISA/Western blot tests look for antibodies to viral proteins; these tests are often falsely negative in the first 1–2 months of HIV infection and falsely positive initially in babies born to infected mothers (anti-gp120 crosses placenta).

AIDS diagnosis = < 200 CD4+, HIV positive with AIDS indicator condition (e.g., PCP), or CD4/CD8 ratio < 1.5.

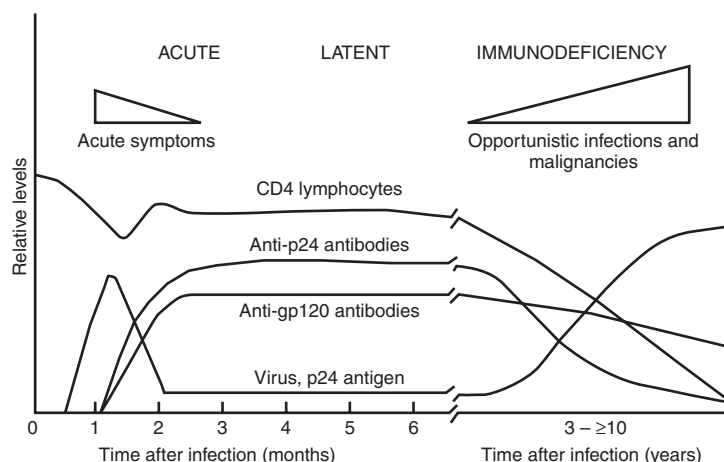
**HIV immunity**

CCR5 mutation

Homozygous = immunity.  
Heterozygous = slower course.  
Rapid progression to AIDS.

1% of U.S. Caucasians.  
20% of U.S. Caucasians.

CXCR1 mutation

► MICROBIOLOGY–VIROLOGY (*continued*)**Time course of HIV infection**

(Adapted, with permission, from Levinson W. *Medical Microbiology and Immunology: Examination and Board Review*, 8th ed. New York: McGraw-Hill, 2004:318.)

**Opportunistic infections and disease in AIDS**

Organ system	Infection/disease
Brain	Cryptococcal meningitis, toxoplasmosis, CMV encephalopathy, AIDS dementia, PML (JC virus)
Eyes	CMV retinitis
Mouth and throat	Thrush ( <i>Candida albicans</i> ), HSV, CMV, oral hairy leukoplakia (EBV)
Lungs	<i>Pneumocystis carinii</i> pneumonia (PCP), TB, histoplasmosis
GI	Cryptosporidiosis, <i>Mycobacterium avium–intracellulare</i> complex, CMV colitis, non-Hodgkin's lymphoma (EBV)
Skin	Shingles (VZV), Kaposi's sarcoma (HHV-8)
Genitals	Genital herpes, warts, and cervical cancer (HPV)

**HIV encephalitis**

Occurs late in the course of HIV infection. Virus gains CNS access via infected macrophages. Microglial nodules with multinucleated giant cells.

**Prions**

Infectious agents that do not contain RNA or DNA (consist only of proteins); encoded by cellular genes. Diseases include Creutzfeldt-Jakob disease (CJD—rapid progressive dementia), kuru, scrapie (sheep), and “mad cow disease.” Prions are associated with spongiform encephalopathy. Normal prions have  $\alpha$ -helix conformation; pathologic prions (like CJD) are  $\beta$ -pleated sheets.

## ► MICROBIOLOGY—SYSTEMS

<b>Normal flora: dominant</b>	Skin— <i>Staphylococcus epidermidis</i> . Nose— <i>S. aureus</i> . Oropharynx—viridans streptococci. Dental plaque— <i>Streptococcus mutans</i> . Colon— <i>Bacteroides fragilis</i> > <i>E. coli</i> . Vagina— <i>Lactobacillus</i> , colonized by <i>E. coli</i> and group B strep.				Neonates delivered by cesarean section have no flora but are rapidly colonized after birth.
<b>Common causes of pneumonia</b>	Children (6 wks–18 yr)	Adults (18–40 yr)	Adults (40–65 yr)	Elderly	
	Viruses (RSV)	<i>Mycoplasma</i>	<i>S. pneumoniae</i>	<i>S. pneumoniae</i>	
	<i>Mycoplasma</i>	<i>C. pneumoniae</i>	<i>H. influenzae</i>	Viruses	
	<i>Chlamydia pneumoniae</i>	<i>S. pneumoniae</i>	Anaerobes	Anaerobes	
	<i>Streptococcus pneumoniae</i>		Viruses	<i>H. influenzae</i>	
			<i>Mycoplasma</i>	Gram-negative rods	
	<b>Special groups:</b>				
	Nosocomial (hospital acquired)	<i>Staphylococcus</i> , gram-negative rods			
	Immunocompromised	<i>Staphylococcus</i> , gram-negative rods, fungi, viruses, <i>Pneumocystis carinii</i> —with HIV			
	Aspiration	Anaerobes			
	Alcoholic/IV drug user	<i>S. pneumoniae</i> , <i>Klebsiella</i> , <i>Staphylococcus</i>			
	Postviral	<i>Staphylococcus</i> , <i>H. influenzae</i>			
	Neonate	Group B streptococci, <i>E. coli</i>			
	Atypical	<i>Mycoplasma</i> , <i>Legionella</i> , <i>Chlamydia</i>			
<b>Causes of meningitis</b>	Newborn (0–6 mos) →	Children (6 mos–6 yrs) →	6–60 yrs	→ 60 yrs +	
	Group B streptococci	<i>Streptococcus pneumoniae</i>	<i>N. meningitidis</i>	<i>S. pneumoniae</i>	
	<i>E. coli</i>	<i>Neisseria meningitidis</i>	Enteroviruses	Gram-negative rods	
	<i>Listeria</i>	<i>Haemophilus influenzae</i> type B	<i>S. pneumoniae</i>	<i>Listeria</i>	
		Enteroviruses	HSV		
	In HIV— <i>Cryptococcus</i> , CMV, toxoplasmosis (brain abscess), JC virus (PML).				
	Note: Incidence of <i>H. influenzae</i> meningitis has ↓ greatly with introduction of <i>H. influenzae</i> vaccine in last 10–15 years.				
<b>CSF findings in meningitis</b>	Pressure	Cell type	Protein	Sugar	
Bacterial	↑	↑ PMNs	↑	↓	
Fungal/TB	↑	↑ lymphocytes	↑	↓	
Viral	Normal/↑	↑ lymphocytes	Normal	Normal	

► MICROBIOLOGY—SYSTEMS (*continued*)

<b>Osteomyelitis</b>	<p>Most people—<i>S. aureus</i>.</p> <p>Sexually active—<i>Neisseria gonorrhoeae</i> (rare), septic arthritis more common.</p> <p>Diabetics and drug addicts—<i>Pseudomonas aeruginosa</i>.</p> <p>Sickle cell—<i>Salmonella</i>.</p> <p>Prosthetic replacement—<i>S. aureus</i> and <i>S. epidermidis</i>.</p> <p>Vertebral—<i>Mycobacterium tuberculosis</i> (Pott's disease).</p>	<p>Assume <i>S. aureus</i> if no other information.</p> <p>Most osteomyelitis occurs in children.</p> <p>Elevated ESR.</p>
<b>Urinary tract infections</b>	<p>Ambulatory—<i>E. coli</i> (50–80%), <i>Klebsiella</i> (8–10%). <i>Staphylococcus saprophyticus</i> (10–30%) is the 2nd most common cause of UTI in young ambulatory women.</p> <p>Hospital—<i>E. coli</i>, <i>Proteus</i>, <i>Klebsiella</i>, <i>Serratia</i>, <i>Pseudomonas</i>.</p> <p>Epidemiology: women to men—10:1 (short urethra colonized by fecal flora).</p> <p>Predisposing factors: flow obstruction, kidney surgery, catheterization, gynecologic abnormalities, diabetes, and pregnancy.</p>	<p>UTIs mostly caused by ascending infections. In males: babies with congenital defects; elderly with enlarged prostates.</p> <p>UTI—dysuria, frequency, urgency, suprapubic pain.</p> <p>Pyelonephritis—fever, chills, flank pain, and CVA tenderness.</p>
<b>UTI bugs</b>		
<b>Species</b>	<b>Features of the organism</b>	<b>SSEEK PP.</b>
<i>Serratia marcescens</i>	Some strains produce a red pigment; often nosocomial and drug resistant.	Diagnostic markers:
<i>Staphylococcus saprophyticus</i>	2nd leading cause of community-acquired UTI in sexually active women.	Leukocyte esterase—positive = bacterial.
<i>Escherichia coli</i>	Leading cause of UTI. Colonies show metallic sheen on EMB agar.	Nitrite test—positive = gram negative.
<i>Enterobacter cloacae</i>	Often nosocomial and drug resistant.	
<i>Klebsiella pneumoniae</i>	Large mucoid capsule and viscous colonies.	
<i>Proteus mirabilis</i>	Motility causes “swarming” on agar; produces urease; associated with struvite stones.	
<i>Pseudomonas aeruginosa</i>	Blue-green pigment and fruity odor; usually nosocomial and drug resistant.	



**Sexually transmitted diseases**

Disease	Clinical features	Organism
Gonorrhea	Urethritis, cervicitis, PID, prostatitis, epididymitis, arthritis, creamy purulent discharge	<i>Neisseria gonorrhoeae</i>
1° syphilis	Painless chancre	<i>Treponema pallidum</i>
2° syphilis	Fever, lymphadenopathy, skin rashes, condylomata lata	
3° syphilis	Gummas, tabes dorsalis, general paresis, aortitis, Argyll Robertson pupil	
Genital herpes	Painful penile, vulvar, or cervical ulcers	HSV-2
Chlamydia	Urethritis, cervicitis, conjunctivitis, Reiter's syndrome, PID	<i>Chlamydia trachomatis</i> (D–K)
Lymphogranuloma venereum	Ulcers, lymphadenopathy, rectal strictures	<i>C. trachomatis</i> (L1–L3)
Trichomoniasis	Vaginitis, strawberry-colored mucosa	<i>Trichomonas vaginalis</i>
AIDS	Opportunistic infections, Kaposi's sarcoma, lymphoma	HIV
Condylomata acuminata	Genital warts, koilocytes	HPV 6 and 11
Hepatitis B	Jaundice	HBV
Chancroid	Painful genital ulcer, inguinal adenopathy	<i>Haemophilus ducreyi</i>
Bacterial vaginosis	Noninflammatory, malodorous discharge (fishy smell); positive whiff test, clue cells	<i>Gardnerella vaginalis</i>

**Pelvic inflammatory disease**

Top bugs—*Chlamydia trachomatis* (subacute, often undiagnosed), *Neisseria gonorrhoeae* (acute, high fever). *C. trachomatis* is the most common STD in the United States (3–4 million cases per year). Cervical motion tenderness (chandelier sign), purulent cervical discharge. PID may include salpingitis, endometritis, hydrosalpinx, and tubo-ovarian abscess.

Salpingitis is a risk factor for ectopic pregnancy, infertility, chronic pelvic pain, and adhesions. Other STDs include *Gardnerella* (clue cells) and *Trichomonas* (motile on wet prep).

**Nosocomial infections**

Risk factor	Pathogen	Notes
Newborn nursery	CMV, RSV	The 2 most common causes of nosocomial infections are <i>E. coli</i> (UTI) and <i>S. aureus</i> (wound infection). Presume <i>Pseudomonas</i> <b>AIR</b> uginosa when <b>AIR</b> or burns are involved.
Urinary catheterization	<i>E. coli</i> , <i>Proteus mirabilis</i>	
Respiratory therapy equipment	<i>Pseudomonas aeruginosa</i>	
Work in renal dialysis unit	HBV	
Hyperalimentation	<i>Candida albicans</i>	
Water aerosols	<i>Legionella</i>	<i>Legionella</i> when water source is involved.

**Infections dangerous in pregnancy**

ToRCHeS = Toxoplasma, Rubella, CMV, HSV/HIV, Syphilis.

## ► MICROBIOLOGY—SYSTEMS (continued)

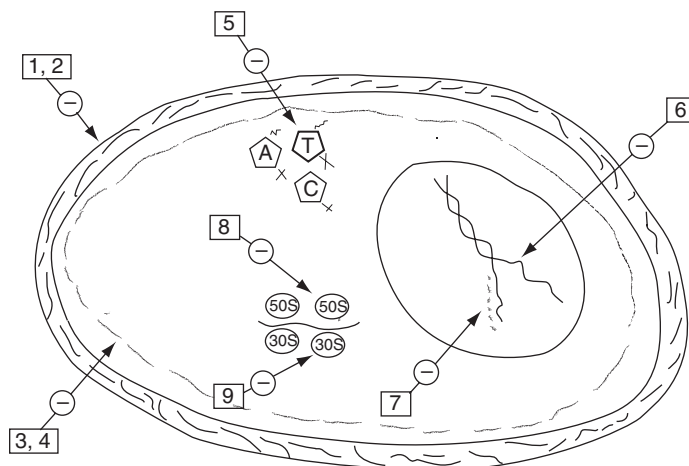
**Bug hints (if all else fails)**

Pus, empyema, abscess—*S. aureus*.  
 Pediatric infection—*Haemophilus influenzae* (including epiglottitis).  
 Pneumonia in cystic fibrosis, burn infection—*Pseudomonas aeruginosa*.  
 Branching rods in oral infection—*Actinomyces israelii*.  
 Traumatic open wound—*Clostridium perfringens*.  
 Surgical wound—*S. aureus*.  
 Dog or cat bite—*Pasteurella multocida*.  
 Currant jelly sputum—*Klebsiella*.  
 Sepsis/meningitis in newborn—group B strep.

## ► MICROBIOLOGY—ANTIMICROBIALS

**Antimicrobial therapy**

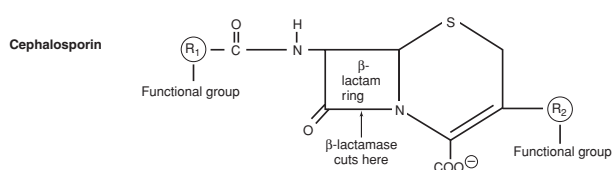
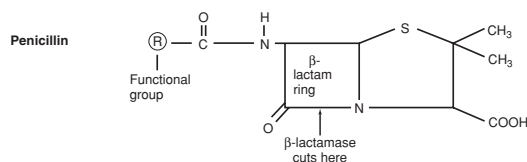
Mechanism of action	Drugs
1. Block cell wall synthesis by inhibition of peptidoglycan cross-linking	Penicillin, ampicillin, ticarcillin, piperacillin, imipenem, aztreonam, cephalosporins
2. Block peptidoglycan synthesis	Bacitracin, vancomycin, cycloserine
3. Disrupt bacterial/fungal cell membranes	Polymyxins
4. Disrupt fungal cell membranes	Amphotericin B, nystatin, fluconazole/azoles
5. Block nucleotide synthesis	Sulfonamides, trimethoprim
6. Block DNA topoisomerases	Quinolones
7. Block mRNA synthesis	Rifampin
8. Block protein synthesis at 50S ribosomal subunit	Chloramphenicol, erythromycin/macrolides, lincomycin, clindamycin, streptogramins (quinupristin, dalfopristin), linezolid
9. Block protein synthesis at 30S ribosomal subunit	Aminoglycosides, tetracyclines



<b>Bactericidal antibiotics</b>	Penicillin, cephalosporins, vancomycin, aminoglycosides, fluoroquinolones, metronidazole.	
<hr/>		
<b>Penicillin</b>	Penicillin G (IV form), penicillin V (oral). Prototype $\beta$ -lactam antibiotics.	
Mechanism	1. Bind penicillin-binding proteins 2. Block transpeptidase cross-linking of cell wall 3. Activate autolytic enzymes	
Clinical use	Bactericidal for gram-positive cocci, gram-positive rods, gram-negative cocci, and spirochetes. Not penicillinase resistant.	
Toxicity	Hypersensitivity reactions, hemolytic anemia.	
<hr/>		
<b>Methicillin, nafcillin, dicloxacillin (penicillinase-resistant penicillins)</b>		
Mechanism	Same as penicillin. Narrow spectrum; penicillinase resistant because of bulkier R group.	
Clinical use	<i>S. aureus</i> (except MRSA; resistant because of altered penicillin-binding protein target site).	
Toxicity	Hypersensitivity reactions; methicillin—interstitial nephritis.	
<hr/>		
<b>Ampicillin, amoxicillin (aminopenicillins)</b>		
Mechanism	Same as penicillin. Wider spectrum; penicillinase sensitive. Also combine with clavulanic acid (penicillinase inhibitor) to enhance spectrum. AmOxicillin has greater Oral bioavailability than ampicillin.	
Clinical use	Extended-spectrum penicillin—certain gram-positive bacteria and gram-negative rods ( <i>Haemophilus influenzae</i> , <i>E. coli</i> , <i>Listeria monocytogenes</i> , <i>Proteus mirabilis</i> , <i>Salmonella</i> , enterococci).	Coverage: ampicillin/ amoxicillin <b>HELPS</b> kill enterococci.
Toxicity	Hypersensitivity reactions; ampicillin rash; pseudomembranous colitis.	
<hr/>		
<b>Ticarcillin, carbenicillin, piperacillin (anti-pseudomonals)</b>		
Mechanism	Same as penicillin. Extended spectrum.	<b>TCP:</b> Takes Care of
Clinical use	<i>Pseudomonas</i> spp. and gram-negative rods; susceptible to penicillinase; use with clavulanic acid.	<i>Pseudomonas</i> .
Toxicity	Hypersensitivity reactions.	

► MICROBIOLOGY—ANTIMICROBIALS (*continued*)**Cephalosporins**

Mechanism	$\beta$ -lactam drugs that inhibit cell wall synthesis but are less susceptible to penicillinases. Bactericidal.	
Clinical use	1st generation (cefazolin, cephalexin)—gram-positive cocci, <i>Proteus mirabilis</i> , <i>E. coli</i> , <i>Klebsiella pneumoniae</i> . 2nd generation (cefoxitin, cefaclor, cefuroxime)—gram-positive cocci, <i>Haemophilus influenzae</i> , <i>Enterobacter aerogenes</i> , <i>Neisseria</i> spp., <i>Proteus mirabilis</i> , <i>E. coli</i> , <i>Klebsiella pneumoniae</i> , <i>Serratia marcescens</i> . 3rd generation (ceftriaxone, cefotaxime, ceftazidime)—serious gram-negative infections resistant to other $\beta$ -lactams; meningitis (most penetrate the blood-brain barrier). Examples: ceftazidime for <i>Pseudomonas</i> ; ceftriaxone for gonorrhea. 4th generation (cefepime, cefpiramide)— $\uparrow$ activity against <i>Pseudomonas</i> and gram-positive organisms.	1st generation— <b>PEcK</b> .  2nd generation— <b>HEN PEcKS</b> .
Toxicity	Hypersensitivity reactions. Cross-hypersensitivity with penicillins occurs in 5–10% of patients. $\uparrow$ nephrotoxicity of aminoglycosides; disulfiram-like reaction with ethanol (in cephalosporins with a methylthiotetrazole group, e.g., cefamandole).	

**Aztreonam**

Mechanism	A monobactam resistant to $\beta$ -lactamases. Inhibits cell wall synthesis (binds to PBP3). Synergistic with aminoglycosides. No cross-allergenicity with penicillins.	
Clinical use	Gram-negative rods— <i>Klebsiella</i> spp., <i>Pseudomonas</i> spp., <i>Serratia</i> spp. No activity against gram-positives or anaerobes. For penicillin-allergic patients and those with renal insufficiency who cannot tolerate aminoglycosides.	
Toxicity	Usually nontoxic; occasional GI upset.	

**Imipenem/cilastatin, meropenem**

Mechanism	Imipenem is a broad-spectrum, $\beta$ -lactamase-resistant carbapenem. Always administered with cilastatin (inhibitor of renal dihydropeptidase I) to $\downarrow$ inactivation in renal tubules.	With imipenem, “the kill is <b>LASTIN</b> ’ with <b>ciLASTATIN</b> .”
Clinical use	Gram-positive cocci, gram-negative rods, and anaerobes. Drug of choice for <i>Enterobacter</i> .	
Toxicity	GI distress, skin rash, and CNS toxicity (seizures) at high plasma levels.	

**Vancomycin**

Mechanism	Inhibits cell wall mucopeptide formation by binding D-ala D-ala portion of cell wall precursors. Bactericidal. Resistance occurs with amino acid change of D-ala D-ala to D-ala D-lac.
Clinical use	Used for serious, gram-positive multidrug-resistant organisms, including <i>S. aureus</i> and <i>Clostridium difficile</i> (pseudomembranous colitis).
Toxicity	Nephrotoxicity, Ototoxicity, Thrombophlebitis, diffuse flushing—"red man syndrome" (can largely prevent by pretreatment with antihistamines and slow infusion rate). Well tolerated in general—does <b>NOT</b> have many problems.

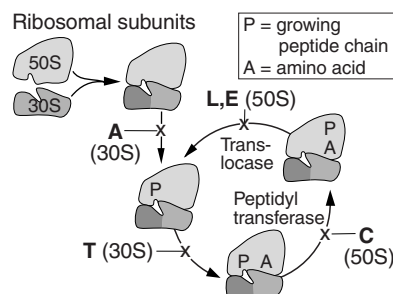
**Protein synthesis inhibitors****30S inhibitors:**

A = Aminoglycosides (streptomycin, gentamicin, tobramycin, amikacin) [bactericidal]  
 T = Tetracyclines [bacteriostatic]

"Buy AT 30, CELL at 50."

**50S inhibitors:**

C = Chloramphenicol [bacteriostatic]  
 E = Erythromycin [bacteriostatic]  
 L = Lincomycin [bacteriostatic]  
 L = cLindamycin [bacteriostatic]

**Aminoglycosides**

	Gentamicin, Neomycin, Amikacin, Tobramycin, Streptomycin.	"Mean" GNATS canNOT kill anaerobes.
Mechanism	Bactericidal; inhibit formation of initiation complex and cause misreading of mRNA. Require O <sub>2</sub> for uptake; therefore ineffective against anaerobes.	
Clinical use	Severe gram-negative rod infections. Synergistic with $\beta$ -lactam antibiotics. Neomycin for bowel surgery.	
Toxicity	Nephrotoxicity (especially when used with cephalosporins), Ototoxicity (especially when used with loop diuretics). Teratogen.	

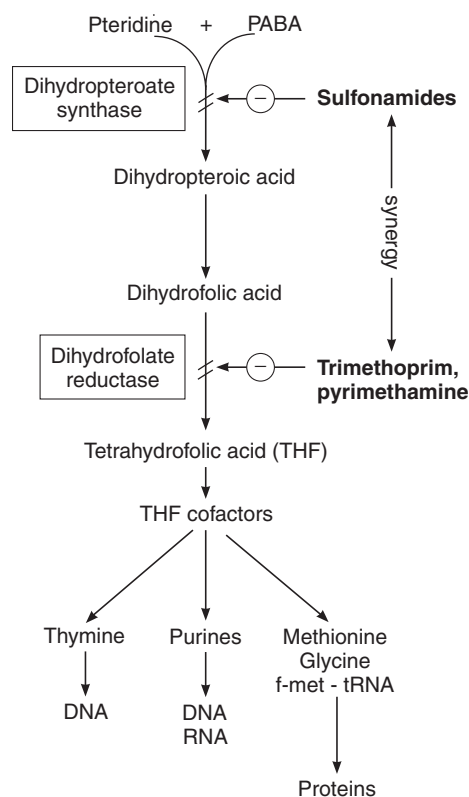
► MICROBIOLOGY—ANTIMICROBIALS (*continued*)

<b>Tetracyclines</b>		
	Tetracycline, doxycycline, demeclocycline, minocycline.	Demeclocycline—ADH antagonist; acts as a Diuretic in SIADH.
Mechanism	Bacteriostatic; bind to 30S and prevent attachment of aminoacyl-tRNA; limited CNS penetration. Doxycycline is fecally eliminated and can be used in patients with renal failure. Must NOT take with milk, antacids, or iron-containing preparations because divalent cations inhibit its absorption in the gut.	
Clinical use	<i>Vibrio cholerae</i> , Acne, <i>Chlamydia</i> , <i>Ureaplasma Urealyticum</i> , <i>Mycoplasma pneumoniae</i> , Tularemia, <i>H. pylori</i> , <i>Borrelia burgdorferi</i> (Lyme disease), <i>Rickettsia</i> .	VACUUM THE BedRoom.
Toxicity	GI distress, discoloration of teeth and inhibition of bone growth in children, photosensitivity. Contraindicated in pregnancy.	
<b>Macrolides</b>		
Mechanism	Erythromycin, azithromycin, clarithromycin. Inhibit protein synthesis by blocking translocation; bind to the 23S rRNA of the 50S ribosomal subunit. Bacteriostatic.	
Clinical use	URIs, pneumonias, STDs—gram-positive cocci (streptococcal infections in patients allergic to penicillin), <i>Mycoplasma</i> , <i>Legionella</i> , <i>Chlamydia</i> , <i>Neisseria</i> .	
Toxicity	GI discomfort (most common cause of noncompliance), acute cholestatic hepatitis, eosinophilia, skin rashes. Increases serum concentration of theophyllines, oral anticoagulants.	
<b>Chloramphenicol</b>		
Mechanism	Inhibits 50S peptidyltransferase. Bacteriostatic.	
Clinical use	Meningitis ( <i>Haemophilus influenzae</i> , <i>Neisseria meningitidis</i> , <i>Streptococcus pneumoniae</i> ). Conservative use owing to toxicities.	
Toxicity	Anemia (dose dependent), aplastic anemia (dose independent), gray baby syndrome (in premature infants because they lack liver UDP-glucuronyl transferase).	
<b>Clindamycin</b>		
Mechanism	Blocks peptide bond formation at 50S ribosomal subunit. Bacteriostatic.	Treats anaerobes above the diaphragm.
Clinical use	Treat anaerobic infections (e.g., <i>Bacteroides fragilis</i> , <i>Clostridium perfringens</i> ).	
Toxicity	Pseudomembranous colitis ( <i>C. difficile</i> overgrowth), fever, diarrhea.	

**Sulfonamides**

Mechanism  
Clinical use  
Toxicity

Sulfamethoxazole (SMX), sulfisoxazole, triple sulfas, sulfadiazine.  
PABA antimetabolites inhibit dihydropteroate synthase. Bacteriostatic.  
Gram-positive, gram-negative, *Nocardia*, *Chlamydia*. Triple sulfas or SMX for simple UTI.  
Hypersensitivity reactions, hemolysis if G6PD deficient, nephrotoxicity (tubulointerstitial nephritis), kernicterus in infants, displace other drugs from albumin (e.g., warfarin).



(Adapted, with permission, from Katzung BG. *Basic and Clinical Pharmacology*, 7th ed. Stamford, CT: Appleton & Lange, 1997:762.)

**Trimethoprim**

Mechanism  
Clinical use

Inhibits bacterial dihydrofolate reductase. Bacteriostatic. Trimethoprim = TMP:  
Used in combination with sulfonamides  
(trimethoprim-sulfamethoxazole [TMP-SMX]),  
causing sequential block of folate synthesis.  
Combination used for recurrent UTIs, *Shigella*,  
*Salmonella*, *Pneumocystis carinii* pneumonia.  
Toxicity  
Megaloblastic anemia, leukopenia, granulocytopenia.  
(May alleviate with supplemental folinic acid.)  
“Treats Marrow Poorly.”

► MICROBIOLOGY–ANTIMICROBIALS (*continued*)

<b>Fluoroquinolones</b>		
	Ciprofloxacin, norfloxacin, ofloxacin, sparfloxacin, moxifloxacin, gatifloxacin, enoxacin (fluoroquinolones), nalidixic acid (a quinolone).	
Mechanism	Inhibit DNA gyrase (topoisomerase II). Bactericidal.	Fluoroquinolones hurt
Clinical use	Gram-negative rods of urinary and GI tracts (including <i>Pseudomonas</i> ), <i>Neisseria</i> , some gram-positive organisms.	attachments to your
		<b>BONES.</b>
Toxicity	GI upset, superinfections, skin rashes, headache, dizziness. Contraindicated in pregnant women and in children because animal studies show damage to cartilage. Tendonitis and tendon rupture in adults; leg cramps and myalgias in kids.	
<b>Metronidazole</b>		
Mechanism	Forms toxic metabolites in the bacterial cell. Bactericidal.	
Clinical use	Antiprotozoal. <i>Giardia</i> , <i>Entamoeba</i> , <i>Trichomonas</i> , <i>Gardnerella vaginalis</i> , anaerobes ( <i>Bacteroides</i> , <i>Clostridium</i> ). Used with bismuth and amoxicillin (or tetracycline) for “triple therapy” against <i>H. pylori</i> .	<b>GET GAP</b> on the <b>Metro!</b>
		Anaerobic infection below the diaphragm.
Toxicity	Disulfiram-like reaction with alcohol; headache, metallic taste.	
<b>Polymyxins</b>		
	Polymyxin B, polymyxin E.	<b>’MYXins MIX up</b> membranes.
Mechanism	Bind to cell membranes of bacteria and disrupt their osmotic properties. Polymyxins are cationic, basic proteins that act like detergents.	
Clinical use	Resistant gram-negative infections.	
Toxicity	Neurotoxicity, acute renal tubular necrosis.	
<b>Anti-TB drugs</b>		
	Streptomycin, Pyrazinamide, Isoniazid (INH), Rifampin, Ethambutol.	<b>INH-SPIRE</b> (inspire).
	Cycloserine (2nd-line therapy).	Isoniazid (INH) used alone for TB prophylaxis; all used in combination for TB treatment.
		All are hepatotoxic.
<b>Isoniazid (INH)</b>		
Mechanism	↓ synthesis of mycolic acids.	<b>INH Injures Neurons and</b>
Clinical use	<i>Mycobacterium tuberculosis</i> . The only agent used as solo prophylaxis against TB.	<b>Hepatocytes.</b>
		Different INH half-lives in fast
Toxicity	Hemolysis if G6PD deficient, neurotoxicity, hepatotoxicity, SLE-like syndrome. Pyridoxine (vitamin B <sub>6</sub> ) can prevent neurotoxicity.	vs. slow acetylators.



**Rifampin**

Mechanism	Inhibits DNA-dependent RNA polymerase.
Clinical use	<i>Mycobacterium tuberculosis</i> ; delays resistance to dapsone when used for leprosy. Used for meningococcal prophylaxis and chemoprophylaxis in contacts of children with <i>Haemophilus influenzae</i> type B.
Toxicity	Minor hepatotoxicity and drug interactions (↑ P-450).

**Rifampin's 4 R's:**

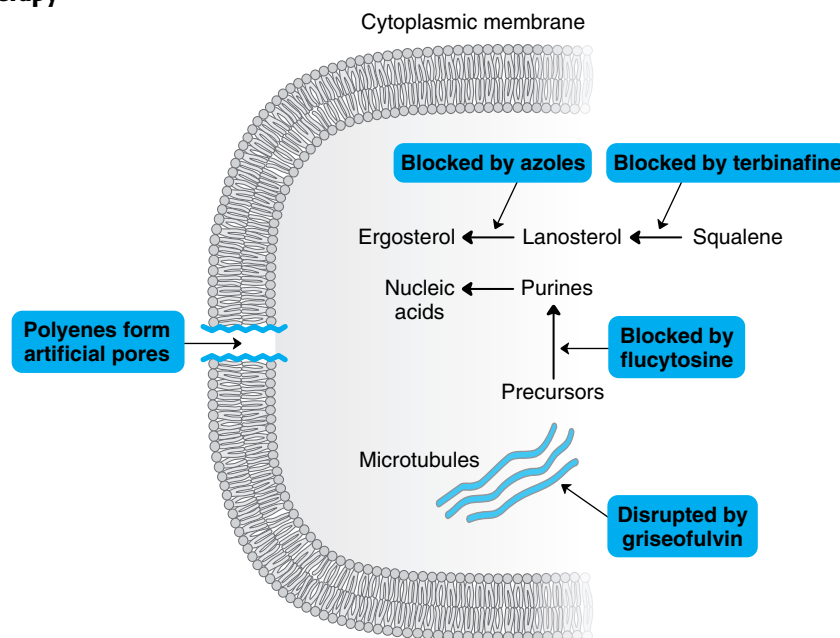
RNA polymerase inhibitor  
 Revs up microsomal P-450  
 Red/orange body fluids  
 Rapid resistance if used alone

**Resistance mechanisms for various antibiotics**

Drug	Most common mechanism
Penicillins/ cephalosporins	β-lactamase cleavage of β-lactam ring
Aminoglycosides	Modification via acetylation, adenylation, or phosphorylation
Vancomycin	Terminal D-ala of cell wall component replaced with D-lac; ↓ affinity.
Chloramphenicol	Modification via acetylation
Macrolides	Methylation of rRNA near erythromycin's ribosome-binding site
Tetracycline	↓ uptake or ↑ transport out of cell
Sulfonamides	Altered enzyme (bacterial dihydropteroate synthetase), ↓ uptake, or ↑ PABA synthesis

**Nonsurgical antimicrobial prophylaxis**

Meningococcal infection	Rifampin (drug of choice), minocycline.
Gonorrhea	Ceftriaxone.
Syphilis	Benzathine penicillin G.
History of recurrent UTIs	TMP-SMX.
<i>Pneumocystis carinii</i> pneumonia	TMP-SMX (drug of choice), aerosolized pentamidine.
Endocarditis with surgical or dental procedures	Penicillins.

► MICROBIOLOGY–ANTIMICROBIALS (*continued*)**Antifungal therapy**

(Adapted, with permission, from Katzung BG, Trevor AJ. *USMLE Road Map: Pharmacology*, 1st ed. New York: McGraw-Hill, 2003:120.)

**Amphotericin B**

Mechanism	Binds ergosterol (unique to fungi); forms membrane pores that allow leakage of electrolytes and disrupt homeostasis.	Amphotericin “tears” holes in the fungal membrane by forming pores.
Clinical use	Used for wide spectrum of systemic mycoses. <i>Cryptococcus</i> , <i>Blastomyces</i> , <i>Coccidioides</i> , <i>Aspergillus</i> , <i>Histoplasma</i> , <i>Candida</i> , <i>Mucor</i> (systemic mycoses). Intrathecally for fungal meningitis; does not cross blood-brain barrier.	
Toxicity	Fever/chills (“shake and bake”), hypotension, nephrotoxicity, arrhythmias, anemia, IV phlebitis (“amphoterrible”). Hydration reduces nephrotoxicity.	

**Nystatin**

Mechanism	Binds to ergosterol, disrupting fungal membranes. Too toxic for systemic use.
Clinical use	“Swish and swallow” for oral candidiasis (thrush); topical for diaper rash or vaginal candidiasis.

**Fluconazole, ketoconazole, clotrimazole, miconazole, itraconazole, voriconazole**

Mechanism	Inhibit fungal steroid (ergosterol) synthesis.
Clinical use	Systemic mycoses. Fluconazole for cryptococcal meningitis in AIDS patients and candidal infections of all types (i.e., yeast infections). Ketoconazole for <i>Blastomyces</i> , <i>Coccidioides</i> , <i>Histoplasma</i> , <i>Candida albicans</i> ; hypercortisolism.
Toxicity	Hormone synthesis inhibition (gynecomastia), liver dysfunction (inhibits cytochrome P-450), fever, chills.

**Flucytosine**

Mechanism	Inhibits DNA synthesis by conversion to fluorouracil, which competes with uracil.
Clinical use	Used in systemic fungal infections (e.g., <i>Candida</i> , <i>Cryptococcus</i> ).
Toxicity	Nausea, vomiting, diarrhea, bone marrow suppression.

**Caspofungin**

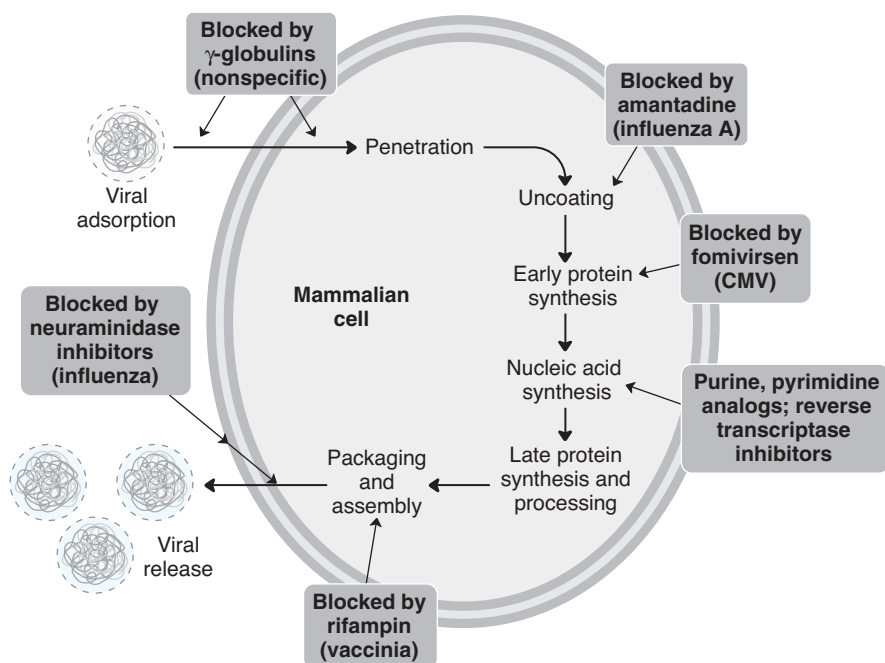
Mechanism	Inhibits cell wall synthesis.
Clinical use	Invasive aspergillosis.
Toxicity	GI upset, flushing.

**Terbinafine**

Mechanism	Inhibits the fungal enzyme squalene epoxidase.
Clinical use	Used to treat dermatophytoses (especially onychomycosis).

**Griseofulvin**

Mechanism	Interferes with microtubule function; disrupts mitosis. Deposits in keratin-containing tissues (e.g., nails).
Clinical use	Oral treatment of superficial infections; inhibits growth of dermatophytes (tinea, ringworm).
Toxicity	Teratogenic, carcinogenic, confusion, headaches, ↑ P-450 and warfarin metabolism.

**Antiviral chemotherapy**

(Adapted, with permission, from Katzung BG, Trevor AJ. *USMLE Road Map: Pharmacology*, 1st ed. New York: McGraw-Hill, 2003:120.)

► MICROBIOLOGY–ANTIMICROBIALS (*continued*)**Amantadine**

Mechanism	Blocks viral penetration/uncoating (M2 protein); may buffer pH of endosome. Also causes the release of dopamine from intact nerve terminals.	“A man to dine” takes off his coat.
Clinical use	Prophylaxis and treatment for influenza A; Parkinson’s disease.	Amantadine blocks influenza A and rubella and causes problems with the cerebellum.
Toxicity	Ataxia, dizziness, slurred speech.	Rimantidine is a derivative with fewer CNS side effects.
Mechanism of resistance	Mutated M2 protein. In 2006, 90% of influenza A were resistant to amantadine.	Does not cross the BBB.

**Zanamivir, oseltamivir**

Mechanism	Inhibit influenza neuraminidase. So release of progeny virus is decreased.
Clinical use	Both influenza A and B.

**Ribavirin**

Mechanism	Inhibits synthesis of guanine nucleotides by competitively inhibiting IMP dehydrogenase.
Clinical use	RSV, chronic hepatitis C.
Toxicity	Hemolytic anemia. Severe teratogen.

**Acyclovir**

Mechanism	Preferentially inhibits viral DNA polymerase when phosphorylated by viral thymidine kinase.
Clinical use	HSV, VZV, EBV. Mucocutaneous and genital herpes lesions. Prophylaxis in immunocompromised patients.
Toxicity	Delirium, tremor, nephrotoxicity.
Mechanism of resistance	Lack of thymidine kinase.

**Ganciclovir**

Mechanism	Phosphorylation by viral kinase; preferentially inhibits CMV DNA polymerase.
Clinical use	CMV, especially in immunocompromised patients.
Toxicity	Leukopenia, neutropenia, thrombocytopenia, renal toxicity. More toxic to host enzymes than acyclovir.
Mechanism of resistance	Mutated CMV DNA polymerase or lack of thymidine kinase.

**Foscarnet**

Mechanism	Viral DNA polymerase inhibitor that binds to the pyrophosphate binding site of the enzyme. Does not require activation by viral kinase.	FOScarnet = pyroFOSphate analog.
Clinical use	CMV retinitis in immunocompromised patients when ganciclovir fails; acyclovir-resistant HSV.	
Toxicity	Nephrotoxicity.	
Mechanism of resistance	Mutated DNA polymerase.	

**HIV therapy**

<b>Protease inhibitors</b>	Saquinavir, ritonavir, indinavir, nelfinavir, amprenavir.	<b>Never (navir) tease a pro—protease inhibitors.</b>
Mechanism	Inhibit assembly of new virus by blocking protease in progeny virions.	
Toxicity	GI intolerance (nausea, diarrhea), hyperglycemia, lipodystrophy, thrombocytopenia (indinavir).	
<b>Reverse transcriptase inhibitors</b>		
Nucleosides	Zidovudine (AZT), didanosine (ddI), zalcitabine (ddC), stavudine (d4T), lamivudine (3TC), abacavir.	<b>Never Ever Deliver nucleosides.</b>
Non-nucleosides	Nevirapine, efavirenz, delavirdine.	
Mechanism	Preferentially inhibit reverse transcriptase of HIV; prevent incorporation of viral genome into host DNA.	
Toxicity	Bone marrow suppression (neutropenia, anemia), peripheral neuropathy, lactic acidosis (nucleosides), rash (non-nucleosides), megaloblastic anemia (AZT).	
Clinical use	Highly active antiretroviral therapy (HAART) generally entails combination therapy with protease inhibitors and reverse transcriptase inhibitors. Initiated when patients have low CD4 counts ( $< 500$ cells/mm <sup>3</sup> ) or high viral load. AZT is used during pregnancy to reduce risk of fetal transmission.	

**Interferons**

Mechanism	Glycoproteins from human leukocytes that block various stages of viral RNA and DNA synthesis. Induce ribonuclease that degrades viral mRNA.
Clinical use	IFN- $\alpha$ —chronic hepatitis B and C, Kaposi's sarcoma. IFN- $\beta$ —MS. IFN- $\gamma$ —NADPH oxidase deficiency.
Toxicity	Neutropenia.

► MICROBIOLOGY—ANTIMICROBIALS (*continued*)**Antiparasitic drugs**

Ivermectin	Onchocerciasis (rIVER blindness treated with IVERmectin).
Mebendazole/ thiabendazole	Nematode/roundworm (e.g., pinworm, whipworm) infections.
Pyrantel pamoate	Giant roundworm ( <i>Ascaris</i> ), hookworm ( <i>Necator/Ancylostoma</i> ), pinworm ( <i>Enterobius</i> ).
Praziquantel	Trematode/fluke (e.g., schistosomes, <i>Paragonimus</i> , <i>Clonorchis</i> ) and cysticercosis.
Niclosamide	Cestode/tapeworm (e.g., <i>Diphyllobothrium latum</i> , <i>Taenia</i> species) infections except cysticercosis.
Pentavalent antimony	Leishmaniasis.
Chloroquine, quinine, mefloquine, atovaquone, proguanil	Malaria.
Primaquine	Latent hypnozoite (liver) forms of malaria ( <i>Plasmodium vivax</i> , <i>P. ovale</i> ).
Metronidazole	Giardiasis, amebic dysentery ( <i>Entamoeba histolytica</i> ), bacterial vaginitis ( <i>Gardnerella vaginalis</i> ), <i>Trichomonas</i> .
TMP-SMX, pentamidine	<i>Pneumocystis carinii</i> pneumonia prophylaxis.
Nifurtimox	Chagas' disease, American trypanosomiasis ( <i>Trypanosoma cruzi</i> ).
Suramin	African trypanosomiasis (sleeping sickness).

**Antibiotics to avoid  
in pregnancy**

Sulfonamides—kernicterus.  
 Aminoglycosides—ototoxicity.  
 Fluoroquinolones—cartilage damage.  
 Erythromycin—acute cholestatic hepatitis in mom  
 (and clarithromycin—embryotoxic).  
 Metronidazole—mutagenesis.  
 Tetracyclines—discolored teeth, inhibition of bone  
 growth.  
 Ribavirin (antiviral)—teratogenic.  
 Griseofulvin (antifungal)—teratogenic.  
 Chloramphenicol—"gray baby."

**SAFE Moms Take Really  
Good Care.**

# HIGH-YIELD PRINCIPLES IN

# Immunology

*"I hate to disappoint you but my rubber lips are immune to your charms."*

—Batman & Robin

*"No State shall abridge the privileges or immunities of its citizens."*

—The Constitution

Immunology can be confusing and complicated, but luckily the USMLE tests only basic principles and facts in this area. Cell surface markers are important to know because they are clinically useful (for example, in identifying specific types of immune deficiency or cancer) and functionally critical to the jobs immune cells carry out. By spending a little extra effort here it is possible to turn a traditionally difficult subject into one that is high yield.

- ▶ High-Yield Clinical Vignettes
- ▶ Lymphoid Structures
- ▶ Lymphocytes
- ▶ Immune Responses

## IMMUNOLOGY—HIGH-YIELD CLINICAL VIGNETTES

- |                                                                                                   |                                             |                                                |
|---------------------------------------------------------------------------------------------------|---------------------------------------------|------------------------------------------------|
| ■ Patient with <i>Mycoplasma pneumoniae</i> exhibits cryoagglutinins during recovery phase.       | What types of immunoglobulins are reacting? | IgM.                                           |
| ■ Young child presents with tetany and candidiasis. Hypocalcemia and immunosuppression are found. | What cell is deficient?                     | T cell (DiGeorge).                             |
| ■ Young child has recurrent lung infections and granulomatous lesions.                            | What is the defect in neutrophils?          | NADPH oxidase (chronic granulomatous disease). |



**Lymph node**

A 2° lymphoid organ that has many afferents, 1 or more efferents. Encapsulated, with trabeculae. Functions are nonspecific filtration by macrophages, storage/proliferation of B and T cells, antibody production.

**Follicle**

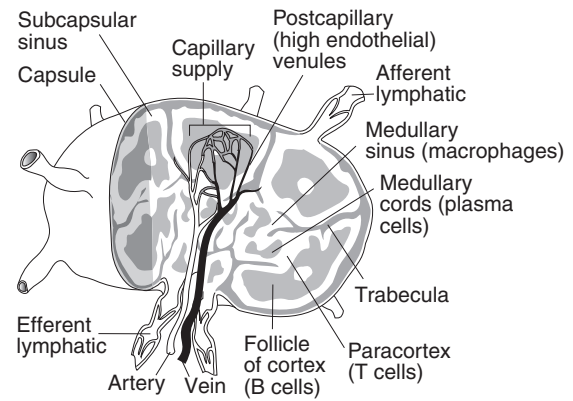
Site of B-cell localization and proliferation. In outer cortex. 1° follicles are dense and dormant. 2° follicles have pale central germinal centers and are active.

**Medulla**

Consists of medullary cords (closely packed lymphocytes and plasma cells) and medullary sinuses. Medullary sinuses communicate with efferent lymphatics and contain reticular cells and macrophages.

**Paracortex**

Houses T cells. Region of cortex between follicles and medulla. Contains high endothelial venules through which T and B cells enter from blood. In an extreme cellular immune response, paracortex becomes greatly enlarged. Not well developed in patients with DiGeorge syndrome.



Paracortex enlarges in an extreme cellular immune response (i.e., viral).

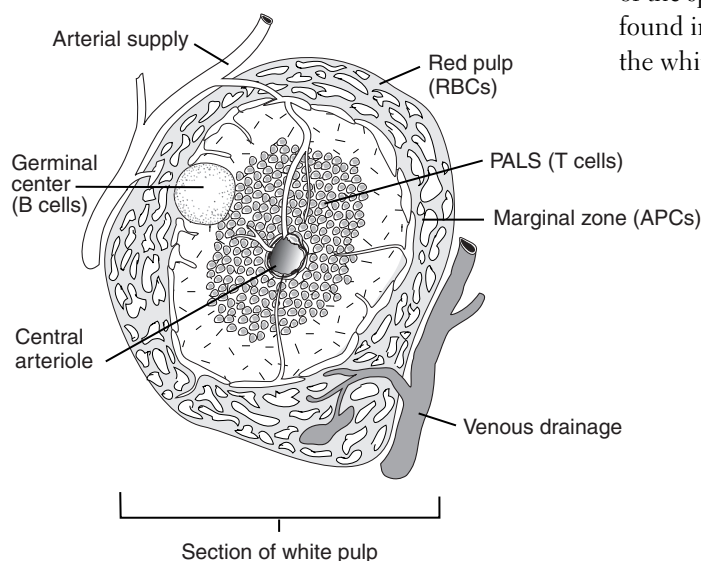
**Lymph drainage**

Right lymphatic duct	Drains right arm and right half of head.
Thoracic duct	Drains everything else.

► IMMUNOLOGY—LYMPHOID STRUCTURES (*continued*)**Sinusoids of spleen**

Long, vascular channels in red pulp with fenestrated “barrel hoop” basement membrane. Macrophages found nearby.

T cells are found in the periarterial lymphatic sheath (PALS) and in the red pulp of the spleen. B cells are found in follicles within the white pulp of the spleen.



(Adapted, with permission, from Janeway CA, Travers P, Walport M, Capra JD. *Immunobiology: The Immune System in Health and Disease*, 4th ed. New York: Garland, 1999.)

**Thymus**

Site of T-cell differentiation and maturation.

Encapsulated. From epithelium of 3rd branchial pouches. Lymphocytes of mesenchymal origin. Cortex is dense with immature T cells; medulla is pale with mature T cells and epithelial reticular cells and contains Hassall's corpuscles. Positive (MHC restriction) and negative selection selection (nonreactive to self) occur at the corticomedullary junction.

T cells = Thymus.

B cells = Bone marrow.

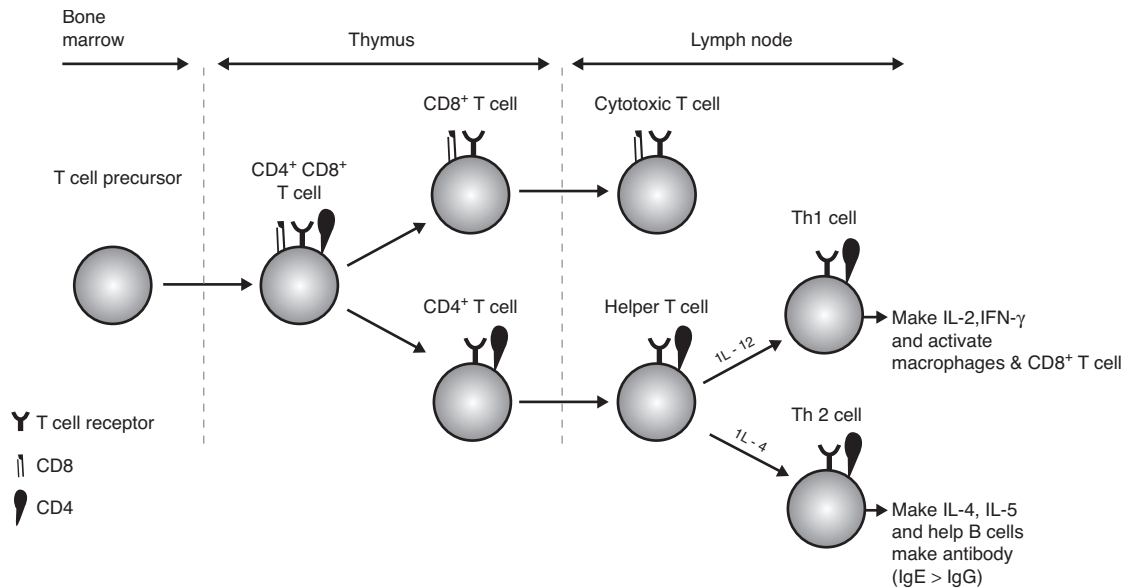
### Innate vs. adaptive immunity

**Innate**—receptors that recognize pathogens are germline encoded. Response to pathogens is fast and non-specific. No memory. Consists of neutrophils, macrophages, dendritic cells, and complement.

**Adaptive**—receptors that recognize pathogens undergo VDJ recombination during lymphocyte development.

Response is slow on first exposure, but memory response is faster and more robust. Consists of T cells, B cells, and circulating antibody.

### Differentiation of T cells



Th1 cells produce IL-2 and IFN- $\gamma$ , activate macrophages and cytotoxic (CD8<sup>+</sup>) T cells.

Th2 cells produce IL-2, IL-4, and IL-5; provide help for B cells to make antibody.

### MHC I and II

MHC = major histocompatibility complex, encoded by **Human Leukocyte Antigen (HLA)** genes.

MHC I = HLA-A, HLA-B, HLA-C.

Expressed on almost all nucleated cells.

Antigen is loaded in RER of mostly intracellular peptides.

Mediates viral immunity.

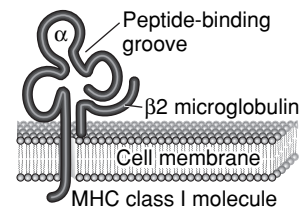
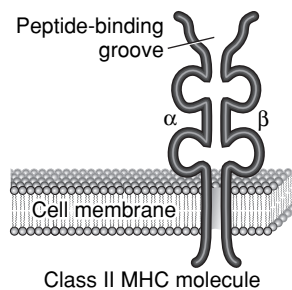
Pairs with  $\beta_2$ -microglobulin.

MHC II = HLA-DR, HLA-DP, HLA-DQ.

Expressed only on antigen presenting cells (APCs).

Antigen is loaded in an acidified endosome.

Main determinants of organ rejection.



► IMMUNOLOGY—LYMPHOCYTES (*continued*)

### Major function of B and T cells

#### B cells

Make antibody

IgG antibodies opsonize bacteria, viruses

Allergy (type I hypersensitivity): IgE

Antibodies cause organ rejection (fast)

#### T cells

CD4+ T cells help B cells make antibody and produce  $\gamma$ -interferon that activates macrophages.

Kill virus-infected cells directly (CD8+ T cells)

Allergy (type IV hypersensitivity)

Organ rejection (slow)

### T-cell glycoproteins

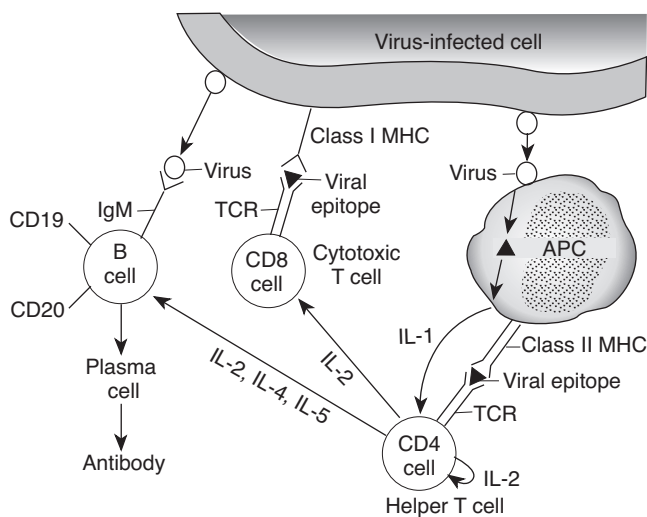
Helper T cells have CD4, which binds to MHC II on antigen-presenting cells. Cytotoxic T cells have CD8, which binds to MHC I on virus-infected cells.

Product of CD and MHC = 8  
(CD4  $\times$  MHC II = 8 = CD8  $\times$  MHC I).

**CD3 complex**—cluster of polypeptides associated with a T-cell receptor. Important in signal transduction.

Antigen-presenting cells:

1. Macrophage
2. B cell
3. Dendritic cell



**T-cell activation**

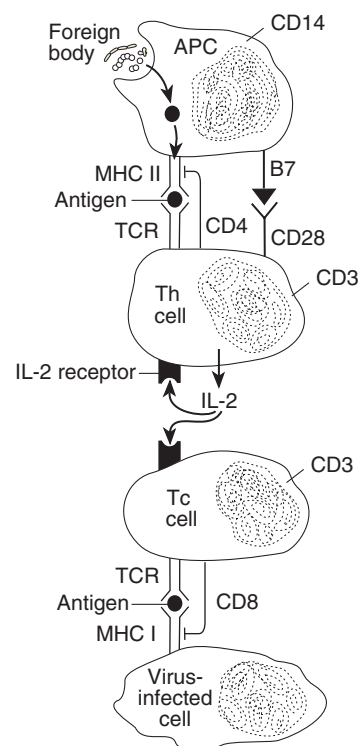
Two signals are required for T cell activation: Signal 1 and Signal 2.

Th activation:

1. Foreign body is phagocytosed by APC
2. Foreign antigen is presented on MHC II and recognized by TCR on Th cell (Signal 1).
3. "Costimulatory signal" is given by interaction of B7 and CD28 (Signal 2).
4. Th cell activated to produce cytokines.

Tc activation:

1. Endogenously synthesized (viral or self) proteins are presented on MHC I and recognized by TCR on Tc cell (Signal 1).
2. IL-2 from Th cell activates Tc cell to kill virus-infected cell (Signal 2).



## ► IMMUNOLOGY– LYMPHOCYTES (continued)

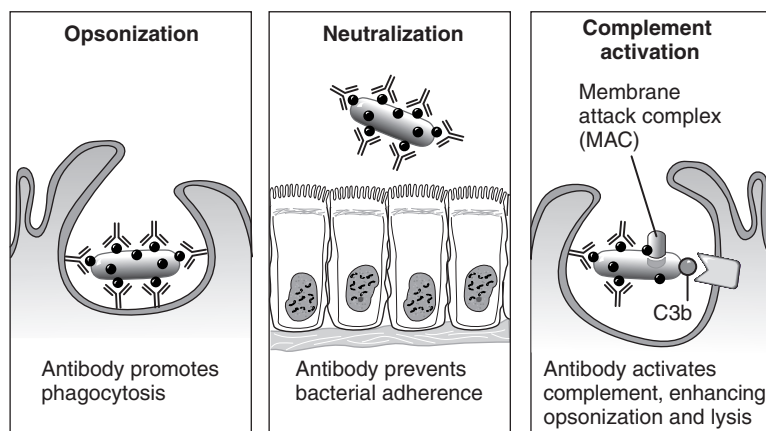
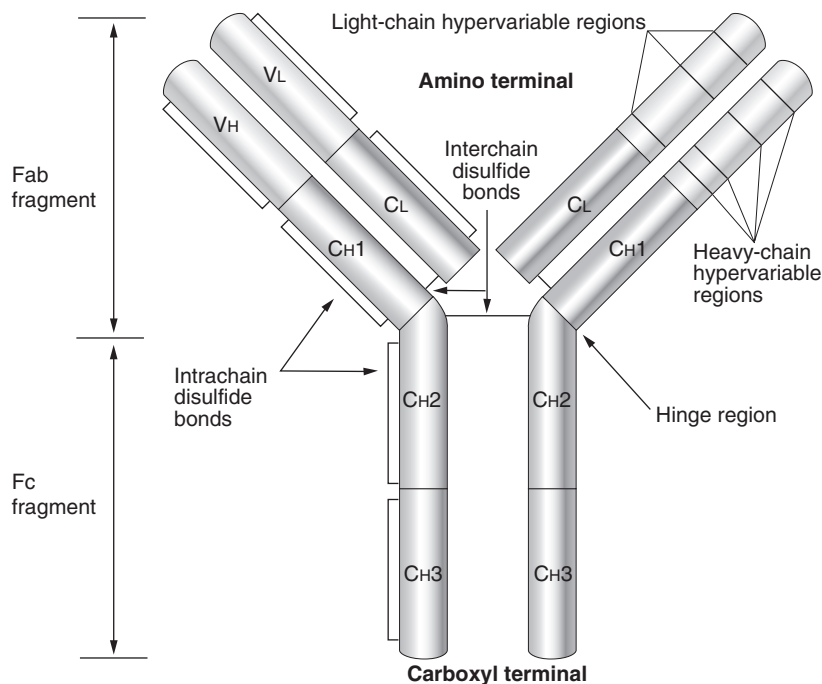
**Antibody structure and function**

Variable part of L and H chains recognizes antigens. Constant part of H chain of IgM and IgG fixes complement. Heavy chain contributes to Fc and Fab fractions. Light chain contributes only to Fab fraction.

Fab: antigen binding fragment

Fc:

Constant  
Carboxy terminal  
Complement-binding  
(IgG + IgM only)  
Carbohydrate  
side chains  
Complement binding  
fragment



Antibody diversity is generated by:

1. Random "recombination" of VJ (light-chain) or VDJ (heavy-chain) genes
2. Random combination of heavy chains with light chains
3. Somatic hypermutation
4. Addition of nucleotides to DNA during "genetic recombination" by terminal deoxynucleotidyl transferase

<b>Immunoglobulin isotypes</b>	Mature B lymphocytes express IgM and IgD on their surfaces. They may differentiate by isotype switching (mediated by cytokines and CD40 ligand) into plasma cells that secrete IgA, IgE, or IgG.	
IgG	Main antibody in 2° response. Most abundant. Fixes complement, crosses the placenta, opsonizes bacteria, neutralizes bacterial toxins and viruses.	
IgA	Prevents attachment of bacteria and viruses to mucous membranes, does not fix complement. Monomer or dimer. Found in secretions. Picks up secretory component from epithelial cells before secretion.	
IgM	Produced in the 1° response to an antigen. Fixes complement but does not cross the placenta. Antigen receptor on the surface of B cells. Monomer or pentamer.	
IgD	Unclear function. Found on the surface of many B cells and in serum.	
IgE	Mediates immediate (type I) hypersensitivity by inducing the release of mediators from mast cells and basophils when exposed to allergen. Mediates immunity to worms. Lowest concentration in serum.	
<b>Ig epitopes</b>	<p>Allotype (polymorphism)—Ig epitope that differs among members of same species. Can be on light chain or heavy chain.</p> <p>Isotype (IgG, IgA, etc.)—Ig epitope common to a single class of Ig (5 classes, determined by heavy chain).</p> <p>Idiotypic (specific for a given antigen)—Ig epitope determined by antigen-binding site.</p>	
		<p>Isotype = <i>iso</i> (same). Common to same class.</p> <p>Idiotypic = <i>idio</i> (unique). Hypervariable region is unique.</p>

## ► IMMUNOLOGY—IMMUNE RESPONSES

**Important cytokines**

IL-1	Secreted by macrophages. Stimulates T cells, B cells, neutrophils, fibroblasts, and epithelial cells to grow, differentiate, or synthesize specific products. An endogenous pyrogen.	<b>“Hot T-bone stEak”:</b> IL-1: fever ( <b>hot</b> ) IL-2: stimulates <b>T</b> cells IL-3: stimulates <b>bone</b> marrow IL-4: stimulates <b>IgE</b> production IL-5: stimulates <b>IgA</b> production
IL-2	Secreted by Th cells. Stimulates growth of helper and cytotoxic T cells.	
IL-3	Secreted by activated T cells. Supports the growth and differentiation of bone marrow stem cells. Has a function similar to GM-CSF.	
IL-4	Secreted by Th2 cells. Promotes growth of B cells. Enhances class switching of IgE and IgG.	
IL-5	Secreted by Th2 cells. Promotes differentiation of B cells. Enhances class switching of IgA. Stimulates production and activation of eosinophils.	
IL-6	Secreted by Th cells and macrophages. Stimulates production of acute-phase reactants and immunoglobulins.	
IL-8	Major chemotactic factor for neutrophils.	
IL-10	Secreted by Th2 cells. Stimulates Th2 while inhibiting Th1.	
IL-12	Secreted by B cells and macrophages. Activates NK and Th1 cells.	
$\gamma$ -interferon	Secreted by Th1 cells. Stimulates macrophages.	
TNF- $\alpha$	Secreted by macrophages. $\uparrow$ IL-2 receptor synthesis by Th cells. $\uparrow$ B-cell proliferation. Attracts and activates neutrophils. Stimulates dendritic cell migration to lymph nodes.	

**Cell surface proteins**

Helper T cells	CD4, TCR, CD3, CD28, CD40L.
Cytotoxic T cells	CD8, TCR, CD3.
B cells	IgM, B7, CD19, CD20, CD40, MHC II.
Macrophages	MHC II, CD14. Receptors for Fc and C3b.
NK cells	Receptors for MHC I, CD16, CD56.
All cells except mature red cells	MHC I.



**Complement**

System of proteins that interact to play a role in humoral immunity and inflammation.

Membrane attack complex of complement defends against gram-negative bacteria. Activated by IgG or IgM in the **classic** pathway, and activated by molecules on the surface of microbes (especially endotoxin) in the **alternate** pathway.

C3b and IgG are the two primary opsonins in bacterial defense.

**GM** makes **classic** cars.

C1, C2, C3, C4—viral neutralization.

C3b—opsonization.

C3a, C5a—anaphylaxis.

C5a—neutrophil chemotaxis.

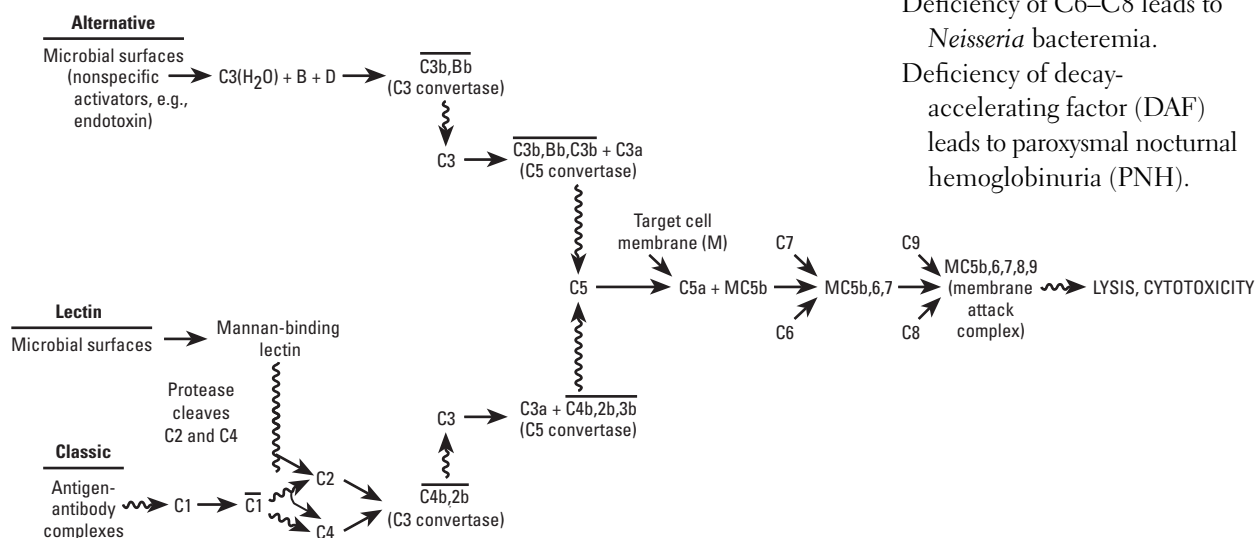
C5b-9—cytolysis by membrane attack complex (MAC).

Deficiency of C1 esterase inhibitor leads to hereditary angioedema (overactive complement).

Deficiency of C3 leads to severe, recurrent pyogenic sinus and respiratory tract infections.

Deficiency of C6–C8 leads to *Neisseria* bacteremia.

Deficiency of decay-accelerating factor (DAF) leads to paroxysmal nocturnal hemoglobinuria (PNH).



(Adapted, with permission, from Levinson W. *Medical Microbiology and Immunology: Examination and Board Review*, 8th ed. New York: McGraw-Hill, 2004:432.)

**Interferon mechanism**

Interferons ( $\alpha$ ,  $\beta$ ,  $\gamma$ ) are proteins that place uninfected cells in an antiviral state. Interferons induce the production of a 2nd protein that inhibits viral protein synthesis by degrading viral mRNA (but not host mRNA).

**Interferes** with viruses:

1.  $\alpha$ - and  $\beta$ -interferons inhibit viral protein synthesis
2.  $\gamma$ -interferons  $\uparrow$  MHC I and II expression and antigen presentation in all cells
3. Activates NK cells to kill virus-infected cells

► IMMUNOLOGY—IMMUNE RESPONSES (*continued*)**Passive vs. active immunity**

Active	Induced after exposure to foreign antigens. Slow onset. Long-lasting protection (memory).	After exposure to Tetanus toxin, Botulinum toxin, HBV, or Rabies, patients are given preformed antibodies (passive)— <b>To Be Healed Rapidly.</b>
Passive	Based on receiving preformed antibodies from another host. Rapid onset. Short life span of antibodies.	

**Antigen variation**

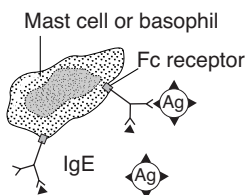
Classic examples: Bacteria— <i>Salmonella</i> (two flagellar variants), <i>Borrelia</i> (relapsing fever), <i>Neisseria gonorrhoeae</i> (pilus protein). Virus—influenza (major = shift, minor = drift). Parasites—trypanosomes (programmed rearrangement).	Some mechanisms for variation include DNA rearrangement and RNA segment rearrangement (e.g., influenza major shift).
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**Anergy**

Self-reactive T cells become nonreactive without costimulatory molecule. B cells also become anergic, but tolerance is less complete than in T cells.
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## Hypersensitivity

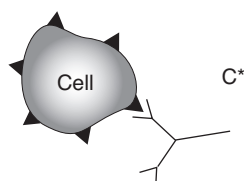
### Type I



**Anaphylactic and atopic**—antigen cross-links IgE on presensitized mast cells and basophils, triggering release of vasoactive amines (i.e., histamine). Reaction develops rapidly after antigen exposure due to preformed antibody.

**First and Fast** (anaphylaxis).  
Types I, II, and III are all antibody mediated.

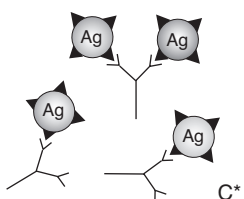
### Type II



**Antibody mediated**—IgM, IgG bind to antigen on “enemy” cell, leading to lysis (by complement) or phagocytosis.

**Cy-2-toxic.**  
Antibody and complement lead to membrane attack complex (MAC).

### Type III



**Immune complex**—antigen-antibody complexes activate complement, which attracts neutrophils; neutrophils release lysosomal enzymes.

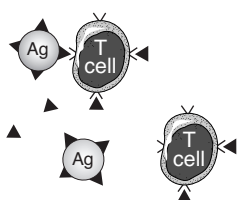
**Serum sickness**—an immune complex disease (type III) in which antibodies to the foreign proteins are produced (takes 5 days). Immune complexes form and are deposited in membranes, where they fix complement (leads to tissue damage). More common than Arthus reaction.

Imagine an immune complex as 3 things stuck together:  
antigen-antibody-complement.  
Most serum sickness is now caused by drugs (not serum).  
Fever, urticaria, arthralgias, proteinuria, lymphadenopathy 5–10 days after antigen exposure.

**Arthus reaction**—a local subacute antibody-mediated hypersensitivity (type III) reaction. Intradermal injection of antigen induces antibodies, which form antigen-antibody complexes in the skin. Characterized by edema, necrosis, and activation of complement.

Antigen-antibody complexes cause the Arthus reaction.

### Type IV



**Delayed (T-cell-mediated) type**—sensitized T lymphocytes encounter antigen and then release lymphokines (leads to macrophage activation).

**4th and last**—delayed. Cell mediated; therefore, it is not transferable by serum.

**4 T's** = T lymphocytes,  
Transplant rejections,  
TB skin tests, Touching (contact dermatitis).

### ACID:

Anaphylactic and Atopic (type I)

Cytotoxic (antibody mediated) (type II)

Immune complex (type III)

Delayed (cell mediated) (type IV)

C\* = complement

► IMMUNOLOGY–IMMUNE RESPONSES (*continued*)**Diseases caused by hypersensitivity**

Type I	Anaphylaxis
	Allergic rhinitis (hay fever)
Type II	Hemolytic anemia
	Idiopathic thrombocytopenic purpura
	Erythroblastosis fetalis
	Rheumatic fever
	Goodpasture's syndrome
	Bullous pemphigoid
	Graves' disease
	Myasthenia gravis
Type III	Lupus
	Rheumatoid arthritis
	Polyarteritis nodosum
	Post-streptococcal glomerulonephritis
	Serum sickness
	Arthus reaction
	Hypersensitivity pneumonitis
Type IV	Type 1 diabetes mellitus
	Multiple sclerosis
	Guillain-Barré syndrome
	Hashimoto's thyroiditis
	Graft-versus-host disease
	PPD (test for <i>M. tuberculosis</i> )
	Contact dermatitis

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**Immune deficiencies****1. ↓ production of:**

B cells—Bruton's agammaglobulinemia	X-linked recessive defect in a tyrosine kinase gene associated with low levels of all classes of immunoglobulins. Associated with recurrent <b>B</b> acterial infections after 6 months of age, when levels of maternal IgG antibody decline. Occurs in <b>B</b> oys (X-linked).
T cells—Thymic aplasia (DiGeorge syndrome)	Thymus and parathyroids fail to develop owing to failure of development of the 3rd and 4th pharyngeal pouches. Presents with <b>T</b> etany owing to hypocalcemia. Recurrent viral and fungal infections due to T-cell deficiency. Congenital defects of heart and great vessels. 22q11 deletion.
B and T cells—severe combined immunodeficiency (SCID)	Defect in early stem-cell differentiation. Presents with recurrent viral, bacterial, fungal, and protozoal infections. May have multiple causes (e.g., failure to synthesize MHC II antigens, defective IL-2 receptors, or adenosine deaminase deficiency).

**2. ↓ activation of:**

T cells—IL-12 receptor deficiency	Presents with disseminated mycobacterial infections.
B cells—hyper-IgM syndrome	Defect in CD40 ligand on CD4 T helper cells leads to inability to class switch. Presents early in life with severe pyogenic infections. High levels of IgM; very low levels of IgG, IgA, and IgE.
B cells—Wiskott-Aldrich syndrome	X-linked defect in the ability to mount an IgM response to capsular polysaccharides of bacteria. Associated with elevated IgA levels, normal IgE levels, and low IgM levels. Triad of symptoms includes recurrent pyogenic <b>I</b> nfections, thrombocytopenic <b>P</b> urpura, <b>E</b> czema ( <b>WIPE</b> ).
Macrophages—Job's syndrome	Failure of $\gamma$ -interferon production by helper T cells. Neutrophils fail to respond to chemotactic stimuli. Presents with recurrent “cold” (noninflamed) staphylococcal abscesses, eczema, coarse facies, retained primary teeth, and high levels of IgE.

**3. Phagocytic cell deficiency:**

Leukocyte adhesion deficiency syndrome	Defect in LFA-1 adhesion proteins on phagocytes. Presents early with severe pyogenic and fungal infections and delayed separation of umbilicus.
Chédiak-Higashi disease	Autosomal recessive. Defect in microtubular function and lysosomal emptying of phagocytic cells. Presents with recurrent pyogenic infections by staphylococci and streptococci, partial albinism, and peripheral neuropathy.
Chronic granulomatous disease	Defect in phagocytosis of neutrophils owing to lack of NADPH oxidase activity or similar enzymes. Presents with marked susceptibility to opportunistic infections with bacteria, especially <i>S. aureus</i> , <i>E. coli</i> , and <i>Aspergillus</i> . Diagnosis confirmed with negative nitroblue tetrazolium dye reduction test.

**4. Idiopathic dysfunction of:**

T cells—chronic mucocutaneous candidiasis	T-cell dysfunction specifically against <i>Candida albicans</i> . Presents with skin and mucous membrane <i>Candida</i> infections.
B cells—selective immunoglobulin deficiency	Deficiency in a specific class of immunoglobulins—possibly due to a defect in isotype switching. Selective IgA deficiency is the most common selective immunoglobulin deficiency. Presents with sinus and lung infections; milk allergies and diarrhea are common.
B cells—ataxia-telangiectasia	Defect in DNA repair enzymes with associated IgA deficiency. Presents with cerebellar problems (ataxia) and spider angiomas (telangiectasia).
B cells—common variable immunodeficiency	Normal numbers of circulating B cells, ↓ plasma cells, ↓ Ig, can be acquired in 20's-30's

► IMMUNOLOGY–IMMUNE RESPONSES (*continued*)

Autoantibodies	Autoantibody	Associated disorder
	Antinuclear antibodies (ANA)	SLE
	Anti-dsDNA, anti-Smith	Specific for SLE
	Antihistone	Drug-induced lupus
	Anti-IgG (rheumatoid factor)	Rheumatoid arthritis
	Antineutrophil (C-ANCA, P-ANCA)	Vasculitis
	Anticentromere	Scleroderma (CREST)
	Anti-Scl-70	Scleroderma (diffuse)
	Antimitochondrial	1° biliary cirrhosis
	Antigliadin	Celiac disease
	Anti-basement membrane	Goodpasture's syndrome
	Anti-epithelial cell	Pemphigus vulgaris
	Antimicrosomal	Hashimoto's thyroiditis
	Anti-Jo-1	Polymyositis, dermatomyositis

**HLA subtypes**

B27	Psoriasis, Ankylosing spondylitis, Inflammatory bowel disease, Reiter's syndrome.	PAIR.
B8	Graves' disease, celiac sprue.	
DR2	Multiple sclerosis, hay fever, SLE, Goodpasture's.	
DR3	Diabetes mellitus type 1.	
DR4	Rheumatoid arthritis, diabetes mellitus type 1.	
DR5	Pernicious anemia → B <sub>12</sub> deficiency, Hashimoto's thyroiditis.	
DR7	Steroid-responsive nephrotic syndrome.	

**Transplant rejection**

Hyperacute rejection	Antibody mediated due to the presence of preformed antidonor antibodies in the transplant recipient. Occurs within minutes after transplantation.
Acute rejection	Cell mediated due to cytotoxic T lymphocytes reacting against foreign MHCs. Occurs weeks after transplantation. Reversible with immunosuppressants such as cyclosporin and OKT3.
Chronic rejection	Antibody-mediated vascular damage (fibrinoid necrosis); occurs months to years after transplantation. Irreversible.
Graft-versus-host disease	Grafted immunocompetent T cells proliferate in the irradiated immunocompromised host and reject cells with "foreign" proteins, resulting in severe organ dysfunction. Major symptoms include a maculopapular rash, jaundice, hepatosplenomegaly, and diarrhea.

# HIGH-YIELD PRINCIPLES IN

## Pathology

*“Digressions, objections, delight in mockery, carefree mistrust are signs of health; everything unconditional belongs in pathology.”*

—Friedrich Nietzsche

The fundamental principles of pathology are key to understanding diseases in all organ systems. Major topics such as inflammation and neoplasia appear frequently in questions aimed at many different organ systems and are definitely high-yield. For example, the concepts of cell injury and inflammation are key to knowing the inflammatory response that follows myocardial infarction, a very common subject of boards questions. Likewise, a familiarity with the early cellular changes that culminate in the development of neoplasias, for example esophageal or colon cancer, is critical. Finally, make sure you recognize the major tumor-associated genes and are comfortable with key cancer concepts like tumor staging and metastasis.

- ▶ Inflammation
- ▶ Neoplasia

## ► PATHOLOGY—INFLAMMATION

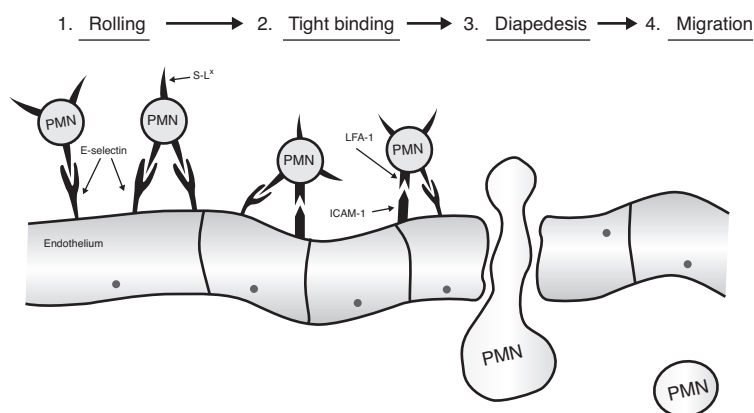
<b>Apoptosis</b>	<p>Programmed cell death.</p> <p>Characterized by cell shrinkage, chromatin condensation, membrane blebbing, and formation of apoptotic bodies, which are then phagocytosed.</p> <p>Occurs during embryogenesis, hormone induction (menstruation), immune cell-mediated death, injurious stimuli (e.g., radiation, hypoxia), atrophy.</p>	
<b>Necrosis</b>	<p>Enzymatic degradation of a cell resulting from exogenous injury.</p> <p>Characterized by enzymatic digestion and protein denaturation, with release of intracellular components.</p> <p>Inflammatory.</p> <p>Morphologically occurs as coagulative (heart, liver, kidney), liquefactive (brain), caseous (tuberculosis), fat (pancreas), fibrinoid, or gangrenous (limbs, GI tract).</p>	
<b>Cell injury</b>	<p><b>Reversible</b></p> <p>Cellular swelling</p> <p>Nuclear chromatin clumping</p> <p>Decreased ATP synthesis</p> <p>Ribosomal detachment</p> <p>Glycogen depletion</p>	<p><b>Irreversible</b></p> <p>Plasma membrane damage</p> <p>Lysosomal rupture</p> <p>Ca<sup>2+</sup> influx → oxidative phosphorylation</p> <p>Nuclear pyknosis, karyolysis, karyorrhexis</p> <p>Mitochondrial permeability</p>
<b>Inflammation</b>	<p>Characterized by <i>rubor</i> (redness), <i>dolor</i> (pain), <i>calor</i> (heat), <i>tumor</i> (swelling), and <i>functio laesa</i> (loss of function).</p>	
Fluid exudation	Increased vascular permeability, vasodilation, endothelial injury	
Leukocyte activation	<p>Emigration (rolling, tight binding, diapedesis)</p> <p>Chemotaxis (bacterial products, complement, chemokines)</p> <p>Phagocytosis and killing</p>	
Fibrosis	<p>Fibroblast emigration and proliferation</p> <p>Deposition of ECM</p>	
Acute	Neutrophil, eosinophil, and antibody mediated	
Chronic	<p>Mononuclear cell mediated:</p> <p>Characterized by persistent destruction and repair</p> <p>Granuloma—nodular collections of macrophages and giant cells</p>	
Resolution	<p>Restoration of normal structure</p> <p>Granulation tissue—highly vascularized, fibrotic</p> <p>Abscess—fibrosis surrounding pus</p> <p>Fistula—abnormal communication</p> <p>Scarring—collagen deposition resulting in altered structure and function</p>	



## Leukocyte extravasation

Neutrophils exit from blood vessels at sites of tissue injury and inflammation in four steps:

1. Rolling—mediated by E-selectin on vascular endothelium binding to Sialyl-Lewis<sup>X</sup> on the leukocyte.
2. Tight binding—mediated by ICAM-1 on vascular endothelium binding to LFA-1 on the leukocyte.
3. Diapedesis—leukocyte travels between endothelial cells and exits blood vessel.
4. Migration—leukocyte travels through the interstitium to the site of injury or infection guided by chemotactic signals (e.g., cytokines).



## Free radical injury

Initiated via radiation exposure, metabolism of drugs (phase I), redox reaction, nitric oxide, transition metals, leukocyte oxidative burst.

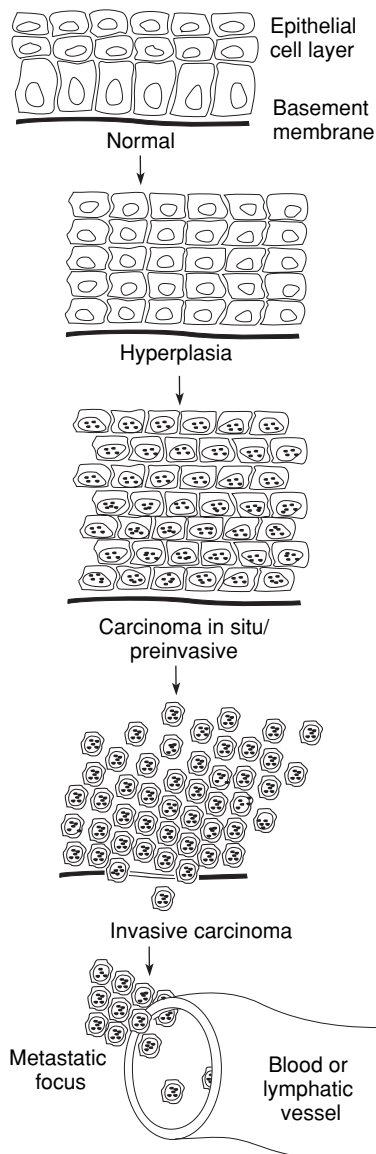
Induces cell injury through membrane lipid peroxidation, protein modification, DNA breakage.

Free radical degradation produced through enzymes (catalase, superoxide dismutase, glutathione peroxidase), spontaneous decay, antioxidants (vitamins E and A).

Reperfusion after anoxia induces free radical production and is a major cause of injury after thrombolytic therapy.

## ▶ PATHOLOGY—NEOPLASIA

## Neoplastic progression



- Normal cells with basal → apical differentiation

- Cells have increased in number—**hyperplasia**
- Abnormal proliferation of cells with loss of size, shape, and orientation—**dysplasia**

- **In situ carcinoma**
- Neoplastic cells have not invaded basement membrane
- High nuclear/cytoplasmic ratio and clumped chromatin
- Neoplastic cells encompass entire thickness

- Cells have invaded basement membrane using **collagenases** and **hydrolases**
- Can metastasize if they reach a blood or lymphatic vessel

- **Metastasis**—spread to distant organ
- Must survive immune attack
- "Seed and soil" theory of metastasis
  - Seed = tumor embolus
  - Soil = target organ—liver, lungs, bone, brain...

(Adapted, with permission, from McPhee S et al. *Pathophysiology of Disease: An Introduction to Clinical Medicine*, 3rd ed. New York: McGraw-Hill, 2000:84.)

**-plasia definitions**

Hyperplasia—↑ in number of cells (reversible).

Metaplasia—1 adult cell type is replaced by another (reversible). Often 2° to irritation and/or environmental exposure (e.g., squamous metaplasia in trachea and bronchi of smokers).

Dysplasia—abnormal growth with loss of cellular orientation, shape, and size in comparison to normal tissue maturation; commonly preneoplastic (reversible).

Anaplasia—abnormal cells lacking differentiation; like primitive cells of same tissue, often equated with undifferentiated malignant neoplasms.

Neoplasia—a clonal proliferation of cells that is uncontrolled and excessive.

**Tumor grade vs. stage**

Grade	Degree of cellular differentiation based on histologic appearance of tumor. Usually graded I–IV based on degree of differentiation and number of mitoses per high-power field; character of tumor itself.	Stage usually has more prognostic value than grade. Stage = Spread. TNM staging system: T = size of Tumor N = Node involvement M = Metastases
Stage	Degree of localization/spread based on site and size of 1° lesion, spread to regional lymph nodes, presence of metastases; spread of tumor in a specific patient.	

**Tumor nomenclature**

Cell type	Benign	Malignant <sup>a</sup>
Epithelium	Adenoma, papilloma	Adenocarcinoma, papillary carcinoma
Mesenchyme		
Blood cells		Leukemia, lymphoma
Blood vessels	Hemangioma	Angiosarcoma
Smooth muscle	Leiomyoma	Leiomyosarcoma
Skeletal muscle	Rhabdomyoma	Rhabdomyosarcoma
Bone	Osteoma	Osteosarcoma
Fat	Lipoma	Liposarcoma
> 1 cell type	Mature teratoma	Immature teratoma

<sup>a</sup>The term **carcinoma** implies epithelial origin, whereas **sarcoma** denotes mesenchymal origin. Both terms imply malignancy.

► PATHOLOGY–NEOPLASIA (*continued*)

Disease associations with neoplasms	Condition	Neoplasm
	1. Down syndrome	1. ALL (we ALL fall Down), AML
	2. Xeroderma pigmentosum, albinism	2. Melanoma and basal, squamous cell carcinomas of skin
	3. Chronic atrophic gastritis, pernicious anemia, postsurgical gastric remnants	3. Gastric adenocarcinoma
	4. Tuberous sclerosis (facial angiofibroma, seizures, mental retardation)	4. Astrocytoma and cardiac rhabdomyoma
	5. Actinic keratosis	5. Squamous cell carcinoma of skin
	6. Barrett's esophagus (chronic GI reflux)	6. Esophageal adenocarcinoma
	7. Plummer-Vinson syndrome (atrophic glossitis, esophageal webs, anemia; all due to iron deficiency)	7. Squamous cell carcinoma of esophagus
	8. Cirrhosis (alcoholic, hepatitis B or C)	8. Hepatocellular carcinoma
	9. Ulcerative colitis	9. Colonic adenocarcinoma
	10. Paget's disease of bone	10. 2° osteosarcoma and fibrosarcoma
	11. Immunodeficiency states	11. Malignant lymphomas
	12. AIDS	12. Aggressive malignant lymphomas (non-Hodgkin's) and Kaposi's sarcoma
	13. Autoimmune diseases (e.g., Hashimoto's thyroiditis, myasthenia gravis)	13. Benign and malignant thymomas
	14. Acanthosis nigricans (hyperpigmentation and epidermal thickening)	14. Visceral malignancy (stomach, lung, breast, uterus)
	15. Dysplastic nevus	15. Malignant melanoma

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<b>Oncogenes</b>	Gain of function → cancer. Need damage to only one allele.
<b>Gene</b>	<b>Associated tumor</b>
<i>abl</i>	CML
<i>c-myc</i>	Burkitt's lymphoma
<i>bcl-2</i>	Follicular and undifferentiated lymphomas (inhibits apoptosis)
<i>erb-B2</i>	Breast, ovarian, and gastric carcinomas
<i>ras</i>	Colon carcinoma
<i>L-myc</i>	Lung tumor
<i>N-myc</i>	Neuroblastoma
<i>ret</i>	Multiple endocrine neoplasia (MEN) types II and III

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<b>Tumor suppressor genes</b>		Loss of function → cancer; both alleles must be lost for expression of disease.
<b>Gene</b>	<b>Chromosome</b>	<b>Associated tumor</b>
<i>Rb</i>	13q	Retinoblastoma, osteosarcoma
<i>BRCA1</i> and 2	17q, 13q	Breast and ovarian cancer
<i>p53</i>	17p	Most human cancers, Li-Fraumeni syndrome
<i>p16</i>	9p	Melanoma
<i>APC</i>	5q	Colorectal cancer
<i>WT1</i>	11q	Wilms' tumor
<i>NF1</i>	17q	Neurofibromatosis type 1
<i>NF2</i>	22q	Neurofibromatosis type 2
<i>DPC</i>	18q	Pancreatic cancer
<i>DCC</i>	18q	Colon cancer

<b>Tumor markers</b>		
PSA (prostatic acid phosphatase)	Prostate-specific antigen. Prostatic carcinoma. Used for screening.	Tumor markers should not be used as the 1° tool for cancer diagnosis. They may be used to confirm diagnosis, to monitor for tumor recurrence, and to monitor response to therapy.
CEA	Carcinoembryonic antigen. Very nonspecific but produced by ~ 70% of colorectal and pancreatic cancers; also produced by gastric and breast carcinomas.	
α-fetoprotein	Normally made by fetus. Hepatocellular carcinomas. Nonseminomatous germ cell tumors of the testis (e.g., yolk sac tumor).	
β-hCG	Hydatidiform moles, Choriocarcinomas, and Gestational trophoblastic tumors.	
CA-125	Ovarian, malignant epithelial tumors.	
S-100	Melanoma, neural tumors, astrocytomas.	
Alkaline phosphatase	Metastases to bone, obstructive biliary disease, Paget's disease of bone.	
Bombesin	Neuroblastoma, lung and gastric cancer.	
TRAP	Tartrate-resistant acid phosphatase. Hairy cell leukemia—a B-cell neoplasm.	
CA-19-9	Pancreatic adenocarcinoma.	

<b>Oncogenic viruses</b>	<b>Virus</b>	<b>Associated cancer</b>
	HTLV-1	Adult T-cell leukemia
	HBV, HCV	Hepatocellular carcinoma
	EBV	Burkitt's lymphoma, nasopharyngeal carcinoma
	HPV	Cervical carcinoma (16, 18), penile/anal carcinoma
	HHV-8 (Kaposi's sarcoma-associated herpesvirus)	Kaposi's sarcoma, body cavity fluid B-cell lymphoma

► **PATHOLOGY—NEOPLASIA (continued)**

<b>Chemical carcinogens</b>	<b>Toxin</b>	<b>Affected organ</b>
	Aflatoxins	Liver (hepatocellular carcinoma)
	Vinyl chloride	Liver (angiosarcoma)
	CCl <sub>4</sub>	Liver (centrilobular necrosis, fatty change)
	Nitrosamines	Esophagus, stomach
	Cigarette smoke	Larynx, lung
	Asbestos	Lung (mesothelioma and bronchogenic carcinoma)
	Arsenic	Skin (squamous cell carcinoma)
	Naphthalene (aniline) dyes	Bladder (transitional cell carcinoma)
	Alkylating agents	Blood (leukemia)

**Paraneoplastic effects of tumors**

<b>Neoplasm</b>	<b>Causes</b>	<b>Effect</b>
Small cell lung carcinoma	ACTH or ACTH-like peptide	Cushing's syndrome
Small cell lung carcinoma and intracranial neoplasms	ADH	SIADH
Squamous cell lung carcinoma, renal cell carcinoma, breast carcinoma, multiple myeloma, and bone metastasis (lysed bone)	PTH-related peptide, TGF- $\beta$ , TNF- $\alpha$ , IL-1	Hypercalcemia
Renal cell carcinoma, hemangioblastoma	Erythropoietin	Polycythemia
Thymoma, small cell lung carcinoma	Antibodies against presynaptic Ca <sup>2+</sup> channels at neuromuscular junction	Lambert-Eaton syndrome (muscle weakness)
Leukemias and lymphomas	Hyperuricemia due to excess nucleic acid turnover (i.e., cytotoxic therapy)	Gout, urate nephropathy

<b>Metastasis to brain</b>	1° tumors that metastasize to brain—Lung, Breast, Skin (melanoma), Kidney (renal cell carcinoma), GI. Overall, approximately 50% of brain tumors are from metastases.	Lots of <b>Bad Stuff Kills Glia</b> . Typically multiple well-circumscribed tumors at gray-white border.
<b>Metastasis to liver</b>	The liver and lung are the most common sites of metastasis after the regional lymph nodes. 1° tumors that metastasize to the liver—Colon > Stomach > Pancreas > Breast > Lung.	Metastases >> 1° liver tumors. Cancer Sometimes Penetrates Benign Liver.
<b>Metastasis to bone</b>	These 1° tumors metastasize to bone—Prostate, Thyroid, Testes, Breast, Lung, Kidney. Metastases from breast and prostate are most common. Metastatic bone tumors are far more common than 1° bone tumors.	<b>P. T. Barnum Loves Kids</b> . Lung = Lytic. Prostate = blastic. Breast = Both lytic and blastic.

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**Cancer epidemiology**

	Male	Female	
Incidence	Prostate (32%) Lung (16%) Colon and rectum (12%)	Breast (32%) Lung (13%) Colon and rectum (13%)	Deaths from lung cancer have plateaued in males but continue to ↑ in females.
Mortality	Lung (33%) Prostate (13%)	Lung (23%) Breast (18%)	Cancer is the 2nd leading cause of death in the United States (heart disease is 1st).

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# HIGH-YIELD PRINCIPLES IN

# Pharmacology

*“Take me, I am the drug; take me, I am hallucinogenic.”*

—Salvador Dali

*“I was under medication when I made the decision not to burn the tapes.”*

—Richard Nixon

Preparation for questions on pharmacology is straightforward. Memorizing all the key drugs and their characteristics (e.g., mechanisms, clinical use, and important side effects) is high yield. Focus on understanding the prototype drugs in each class. Avoid memorizing obscure derivatives. Learn the “classic” and distinguishing toxicities of the major drugs. Do not bother with drug dosages or trade names. Reviewing associated biochemistry, physiology, and microbiology can be useful while studying pharmacology. There is a strong emphasis on ANS, CNS, antimicrobial, and cardiovascular agents as well as on NSAIDs. Much of the material is clinically relevant. Newer drugs on the market are also fair game.

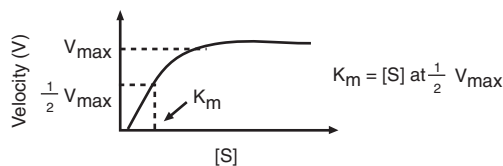
- ▶ High-Yield Clinical Vignettes
- ▶ Pharmacodynamics
- ▶ Autonomic Drugs
- ▶ Toxicities and Side Effects
- ▶ Miscellaneous



## PHARMACOLOGY—HIGH-YIELD CLINICAL VIGNETTES

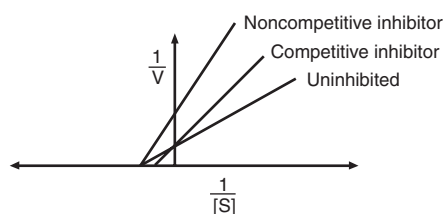
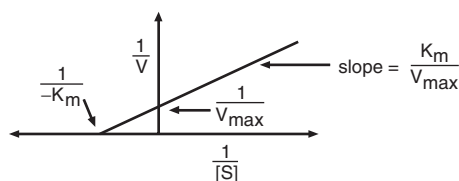
- |                                                                                                                              |                                                             |                                                                                  |
|------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------|----------------------------------------------------------------------------------|
| ■ 28-year-old chemist presents with MPTP exposure.                                                                           | What neurotransmitter is depleted?                          | Dopamine.                                                                        |
| ■ Woman taking tetracycline exhibits photosensitivity.                                                                       | What are the clinical manifestations?                       | Rash on sun-exposed regions of the body.                                         |
| ■ African-American man who goes to Africa develops a hemolytic anemia after taking malarial prophylaxis.                     | What is the enzyme deficiency?                              | Glucose-6-phosphate dehydrogenase.                                               |
| ■ Farmer presents with dyspnea, salivation, miosis, diarrhea, cramping, and blurry vision.                                   | What caused this, and what is the mechanism of action?      | Insecticide poisoning; inhibition of acetylcholinesterase.                       |
| ■ 27-year-old female with a history of psychiatric illness now has urinary retention due to a neuroleptic.                   | What do you treat it with?                                  | Bethanechol.                                                                     |
| ■ Patient with recent kidney transplant is on cyclosporine for immunosuppression. Requires antifungal agent for candidiasis. | What antifungal drug would result in cyclosporine toxicity? | Ketoconazole.                                                                    |
| ■ Patient is on carbamazepine.                                                                                               | What routine workup should always be done?                  | LFTs.                                                                            |
| ■ 23-year-old female who is on rifampin for TB prophylaxis and on birth control (estrogen) gets pregnant.                    | Why?                                                        | Rifampin augments estrogen metabolism in the liver, rendering it less effective. |

## Enzyme kinetics



$K_m$  reflects the affinity of the enzyme for its substrate.  
 $V_{max}$  is directly proportional to the enzyme concentration.  
 The lower the  $K_m$ , the higher the affinity.

The higher the y-intercept, the lower the  $V_{max}$ .  
 The further to the right the x-intercept, the greater the  $K_m$ .



HINT: Competitive inhibitors cross each other competitively, while noncompetitive inhibitors do not.

	Competitive inhibitors	Noncompetitive inhibitors
Resemble substrate	Yes	No
Overcome by $\uparrow [S]$	Yes	No
Bind active site	Yes	No
Effect on $V_{max}$	Unchanged	$\downarrow$
Effect on $K_m$	$\uparrow$	Unchanged

## Pharmacokinetics

Volume of distribution ( $V_d$ )

Relates the amount of drug in the body to the plasma concentration.  $V_d$  of plasma protein-bound drugs can be altered by liver and kidney disease.

$$V_d = \frac{\text{amount of drug in the body}}{\text{plasma drug concentration}}$$

Drugs with:

low  $V_d$  distribute in plasma

medium  $V_d$  distribute in extracellular space

high  $V_d$  distribute in tissues

Clearance (CL)

Relates the rate of elimination to the plasma concentration.

$$CL = \frac{\text{rate of elimination of drug}}{\text{plasma drug concentration}} = V_d \times K_e \text{ (elimination constant)}$$

Half-life ( $t_{1/2}$ )

The time required to change the amount of drug in the body by  $\frac{1}{2}$  during elimination (or during a constant infusion). A drug infused at a constant rate reaches about 94% of steady state after 4  $t_{1/2}$ .

$$t_{1/2} = \frac{0.7 \times V_d}{CL}$$

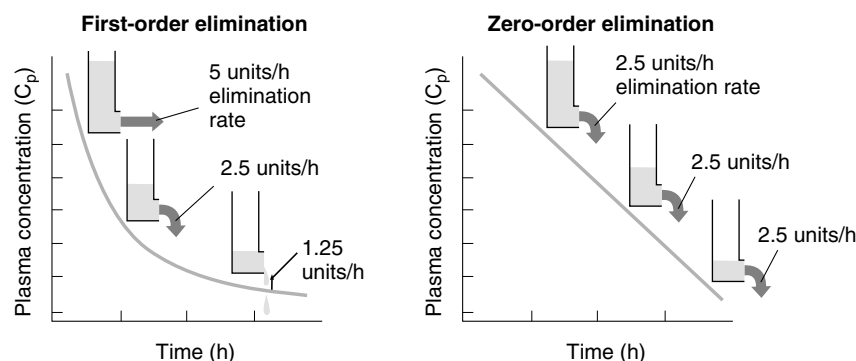
# of half-lives	1	2	3	3.3
Concentration	50%	75%	87.5%	90%

► PHARMACOLOGY–PHARMACODYNAMICS (*continued*)

<b>Dosage calculations</b>	Loading dose = $C_p \times V_d / F$ .	In patients with impaired renal or hepatic function, the loading dose remains unchanged, although the maintenance dose is ↓.
	Maintenance dose = $C_p \times CL / F$ where $C_p$ = target plasma concentration and $F$ = bioavailability = 1 when drug is given IV.	

**Elimination of drugs**

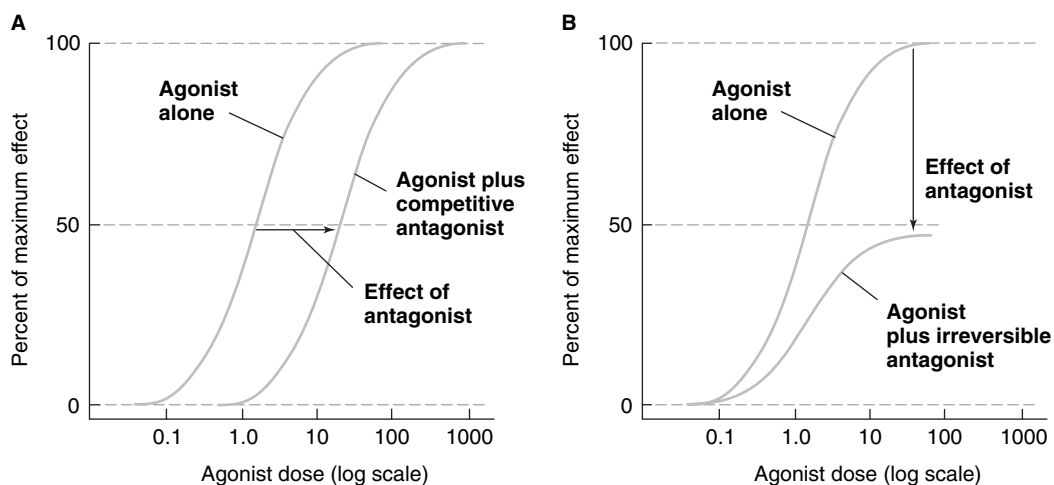
Zero-order elimination	Rate of elimination is constant regardless of $C$ (i.e., constant <b>amount</b> of drug eliminated per unit time). $C_p$ ↓ linearly with time. Examples of drugs—ethanol, phenytoin, and aspirin (at high or toxic concentrations).
First-order elimination	Rate of elimination is proportional to the drug concentration (i.e., constant <b>fraction</b> of drug eliminated per unit time). $C_p$ ↓ exponentially with time.



(Adapted, with permission, from Katzung BG, Trevor AJ. *Pharmacology: Examination & Board Review*, 5th ed. Stamford, CT: Appleton & Lange, 1998:5.)

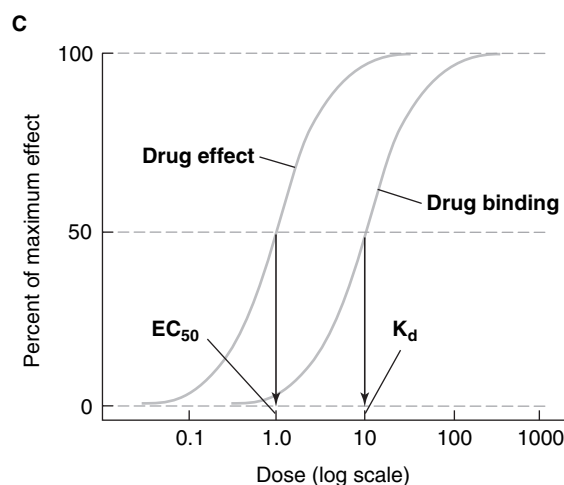
<b>Urine pH and drug elimination</b>	Ionized species get trapped.	
Weak acids	Trapped in basic environments. Digested in acidic environments (below pKa). Treat overdose with bicarbonate.	
Weak bases	Trapped in acidic environments. Digested in basic environments. Treat overdose with ammonium chloride.	
<b>Phase I vs. phase II metabolism</b>	<p>Phase I (reduction, oxidation, hydrolysis) yields slightly polar, water-soluble metabolites (often still active).</p> <p>Phase II (acetylation, glucuronidation, sulfation) yields very polar, inactive metabolites (renally excreted).</p>	<p>Phase I—cytochrome P-450.</p> <p>Phase II—conjugation.</p> <p>Geriatric patients lose phase I first.</p>

## Pharmacodynamics



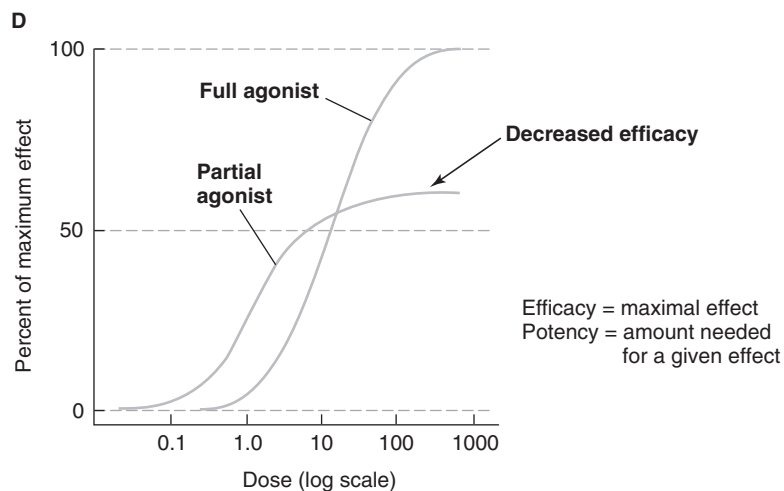
(Adapted, with permission, from Katzung BG, Trevor AJ. *Pharmacology: Examination & Board Review*, 5th ed. Stamford, CT: Appleton & Lange, 1998:13–14.)

A. A competitive antagonist shifts curve to the right, decreasing potency and  $\uparrow$   $EC_{50}$ . B. A noncompetitive antagonist shifts the agonist curve downward, decreasing efficacy.



(Adapted, with permission, from Katzung BG. *Basic and Clinical Pharmacology*, 7th ed. Stamford, CT: Appleton & Lange, 1997:13.)

C. In a system with spare receptors, the  $EC_{50}$  is lower than the  $K_d$ , indicating that to achieve 50% of maximum effect,  $< 50\%$  of the receptors must be activated.  $EC_{50}$ : dose causing 50% of maximal effect.  $K_d$ : concentration of drug required to bind 50% of receptor sites.

► PHARMACOLOGY–PHARMACODYNAMICS (*continued*)Pharmacodynamics (*continued*)

(Adapted, with permission, from Katzung BG. *Basic and Clinical Pharmacology*, 7th ed. Stamford, CT: Appleton & Lange, 1997:13.)

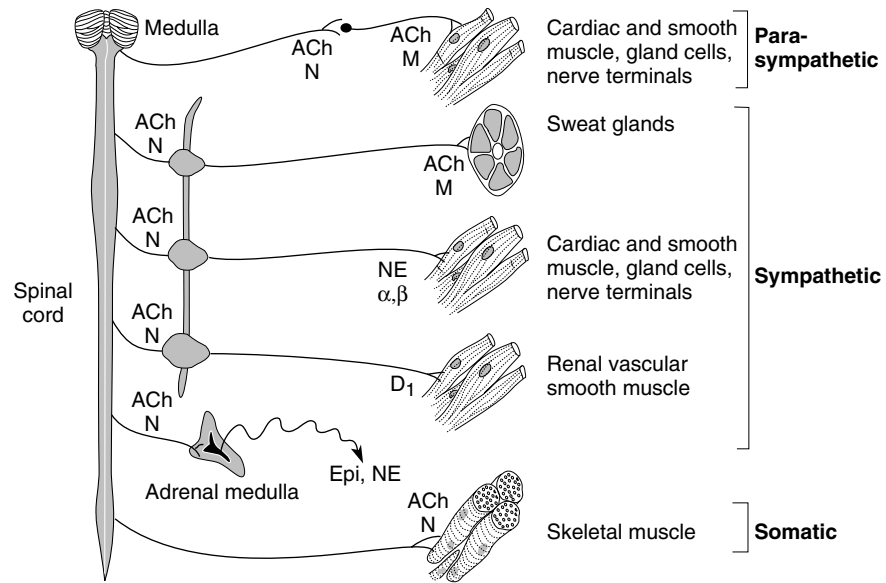
- D. Comparison of dose-response curves for a full agonist and a partial agonist. The **partial agonist** acts on the same receptor system as the full agonist but has a **lower maximal efficacy** no matter the dose. A partial agonist may be more potent (as in the figure), less potent, or equally potent; **potency is an independent factor**.

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**Therapeutic index** 
$$\frac{TD_{50}}{ED_{50}} = \frac{\text{median toxic dose}}{\text{median effective dose}}$$

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## Central and peripheral nervous system

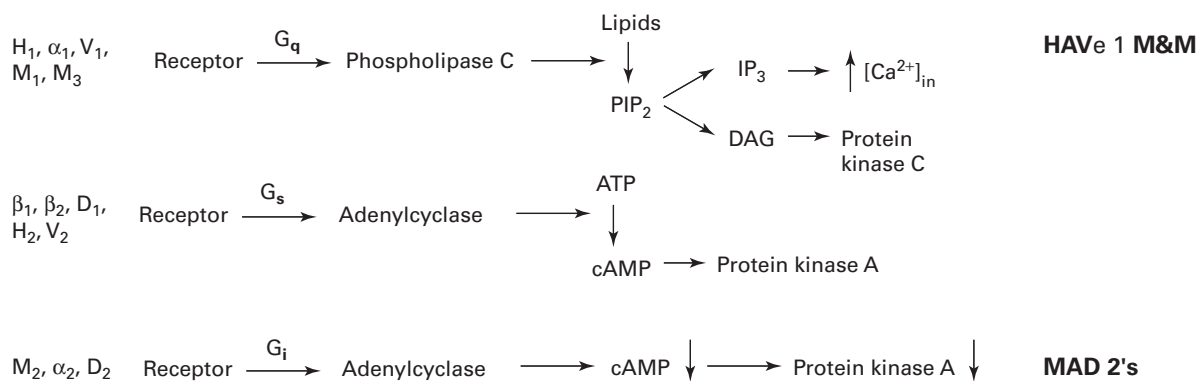


(Adapted, with permission, from Katzung BG. *Basic and Clinical Pharmacology*, 7th ed. Stamford, CT: Appleton & Lange, 1997:74.)

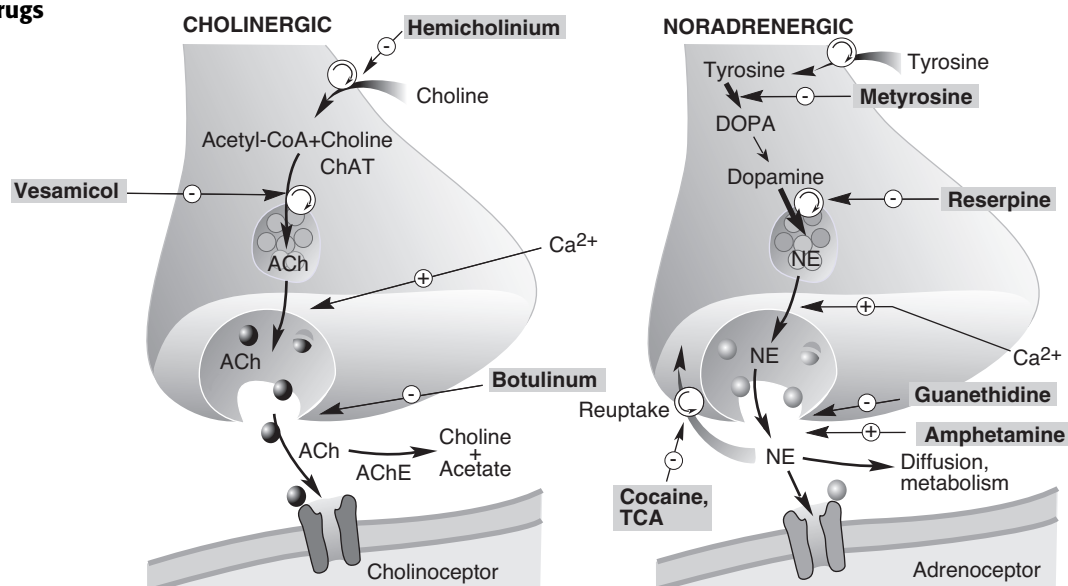
► PHARMACOLOGY—AUTONOMIC DRUGS (*continued*)**G-protein-linked 2nd messengers**

Receptor	G-protein class	Major functions
$\alpha_1$	q	↑ vascular smooth muscle contraction
$\alpha_2$	i	↓ sympathetic outflow, ↓ insulin release
$\beta_1$	s	↑ heart rate, ↑ contractility, ↑ renin release, ↑ lipolysis, ↑ aqueous humor formation
$\beta_2$	s	Vasodilation, bronchodilation, ↑ glucagon release
$M_1$	q	CNS
$M_2$	i	↓ heart rate
$M_3$	q	↑ exocrine gland secretions
$D_1$	s	Relaxes renal vascular smooth muscle
$D_2$	i	Modulates transmitter release, especially in brain
$H_1$	q	↑ nasal and bronchial mucus production, contraction of bronchioles, pruritus, and pain
$H_2$	s	↑ gastric acid secretion
$V_1$	q	↑ vascular smooth muscle contraction
$V_2$	s	↑ $H_2O$ permeability and reabsorption in the collecting tubules of the kidney

"**Q**iss (kiss) and **q**iq (kick) till you're **s**iq (sick) of **s**qs (sex)."

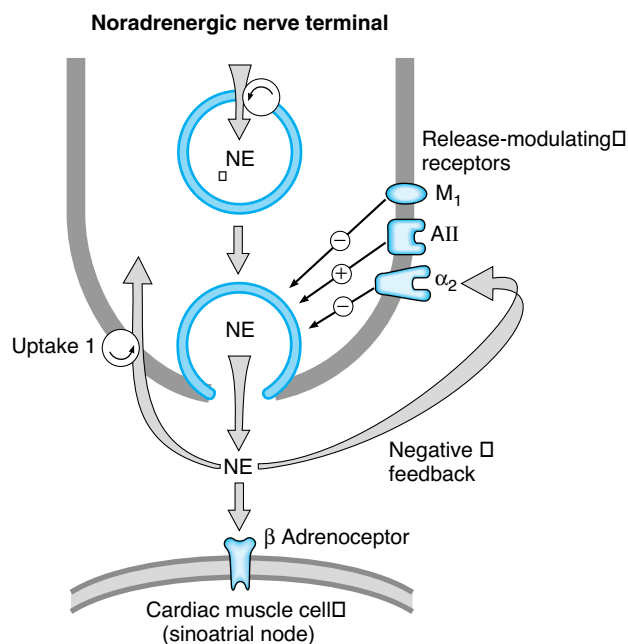


## Autonomic drugs



(Adapted, with permission, from Katzung BG, Trevor AJ. *Pharmacology: Examination & Board Review*, 5th ed. Stamford, CT: Appleton & Lange, 1998:42.)

Circles with rotating arrows represent transporters; ChAT, choline acetyltransferase; ACh, acetylcholine; AChE, acetylcholinesterase; NE, norepinephrine.



(Adapted, with permission, from Katzung BG, Trevor AJ. *Pharmacology: Examination & Board Review*, 5th ed. Stamford, CT: Appleton & Lange, 1998:42.)

Release of NE from a sympathetic nerve ending is modulated by NE itself, acting on presynaptic α<sub>2</sub> autoreceptors, and by ACh, angiotensin II, and other substances.



► PHARMACOLOGY—AUTONOMIC DRUGS (*continued*)**Cholinomimetics**

Drug	Clinical applications	Action
<b>Direct agonists</b>		
Bethanechol	Postoperative and neurogenic ileus and urinary retention	Activates <b>B</b> owel and <b>B</b> ladder smooth muscle; resistant to AChE
Carbachol	Glaucoma, pupillary contraction, and release of intraocular pressure	Contracts ciliary muscle of eye (open angle), pupillary sphincter (narrow angle); resistant to AChE
Pilocarpine	Potent stimulator of sweat, tears, saliva	
Methacholine	Challenge test for diagnosis of asthma	Stimulates muscarinic receptors in airway when inhaled.
<b>Indirect agonists (anticholinesterases)</b>		
Neostigmine	Postoperative and neurogenic ileus and urinary retention, myasthenia gravis, reversal of neuromuscular junction blockade (postoperative)	↑ endogenous ACh No CNS penetration
Pyridostigmine	Myasthenia gravis; does not penetrate CNS	↑ endogenous ACh; ↑ strength
Edrophonium	Diagnosis of myasthenia gravis (extremely short acting)	↑ endogenous ACh
Physostigmine	Glaucoma (crosses blood-brain barrier → CNS) and atropine overdose	↑ endogenous ACh
Echothiophate	Glaucoma	↑ endogenous ACh
<b>Cholinesterase inhibitor poisoning</b>		
	Symptoms include <b>D</b> iarrhea, <b>U</b> rination, <b>M</b> iosis, <b>B</b> ronchospasm, <b>B</b> radycardia, <b>E</b> xcitation of skeletal muscle and CNS, <b>L</b> acrimation, <b>S</b> weating, and <b>S</b> alivation (also abdominal cramping). Antidote—atropine (muscarinic antagonist) plus pralidoxime (chemical antagonist used to regenerate active cholinesterase).	<b>DUMBBELSS.</b> Parathion and other organophosphates.

**Cholinoreceptor blockers**

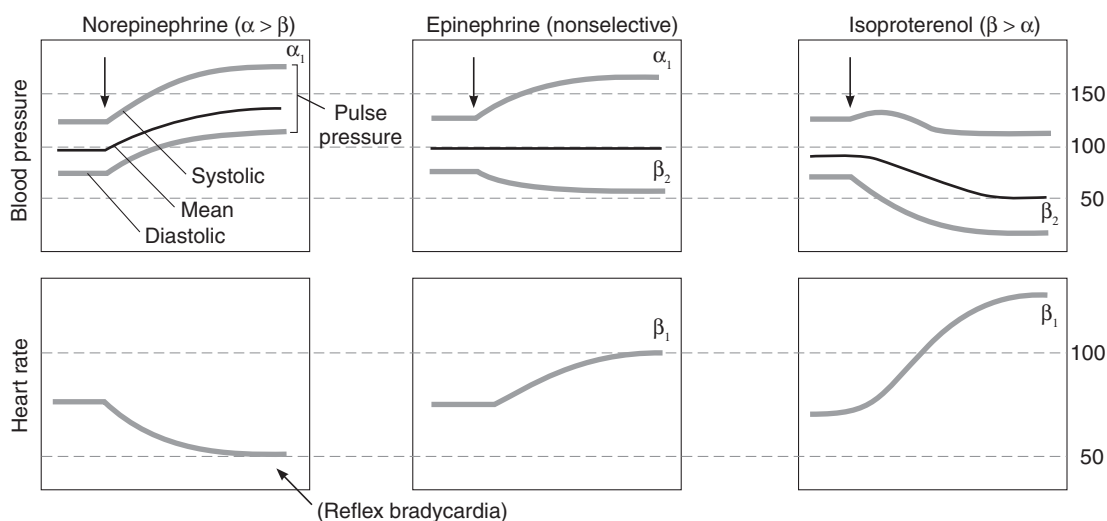
Drug	Organ system	Application
Atropine, homatropine, tropicamide	Eye	Produce mydriasis and cycloplegia
Benztropine	CNS	Parkinson's disease
Scopolamine	CNS	Motion sickness
Ipratropium	Respiratory	Asthma, COPD
Methscopolamine, oxybutin, glycopyrrolate	Genitourinary	Reduce urgency in mild cystitis and reduce bladder spasms

**Glaucoma drugs**

Drug	Mechanism	Side effects
<b><math>\alpha</math>-agonists</b>		
Epinephrine	↑ outflow of aqueous humor	Mydriasis, stinging; do not use in closed-angle glaucoma
Brimonidine	↓ aqueous humor synthesis	No pupillary or vision changes
<b><math>\beta</math>-blockers</b>		
Timolol, betaxolol, carteolol	↓ aqueous humor secretion	No pupillary or vision changes
<b>Diuretics</b>		
Acetazolamide	↓ aqueous humor secretion due to ↓ $\text{HCO}_3^-$ (via inhibition of carbonic anhydrase)	No pupillary or vision changes
<b>Cholinomimetics</b>		
Pilocarpine, carbachol, physostigmine, echothiophate	↑ outflow of aqueous humor; contract ciliary muscle and open trabecular meshwork; use pilocarpine in emergencies; very effective at opening canal of Schlemm	Miosis, cyclospasm
<b>Prostaglandin</b>		
Latanoprost ( $\text{PGF}_{2\alpha}$ )	↑ outflow of aqueous humor	Darkens color of iris (browning)
<b>Atropine</b>		
Organ system	Muscarinic antagonist.	
Eye	↑ pupil dilation, cycloplegia.	Blocks <b>SLUD</b> : Salivation Lacrimation Urination Defecation
Airway	↓ secretions.	
Stomach	↓ acid secretion.	
Gut	↓ motility.	
Bladder	↓ urgency in cystitis.	
Toxicity	↑ body temperature; rapid pulse; dry mouth; dry, flushed skin; cycloplegia; constipation; disorientation. Can cause acute angle-closure glaucoma in elderly, urinary retention in men with prostatic hypertrophy, and hyperthermia in infants.	<b>Side effects:</b> Hot as a hare Dry as a bone Red as a beet Blind as a bat Mad as a hatter
<b>Hexamethonium</b>		
Mechanism	Nicotinic ACh receptor antagonist.	
Clinical use	Ganglionic blocker. Used in experimental models to prevent vagal reflex responses to changes in blood pressure—e.g., prevents reflex bradycardia caused by NE.	

► PHARMACOLOGY—AUTONOMIC DRUGS (*continued*)**Sympathomimetics**

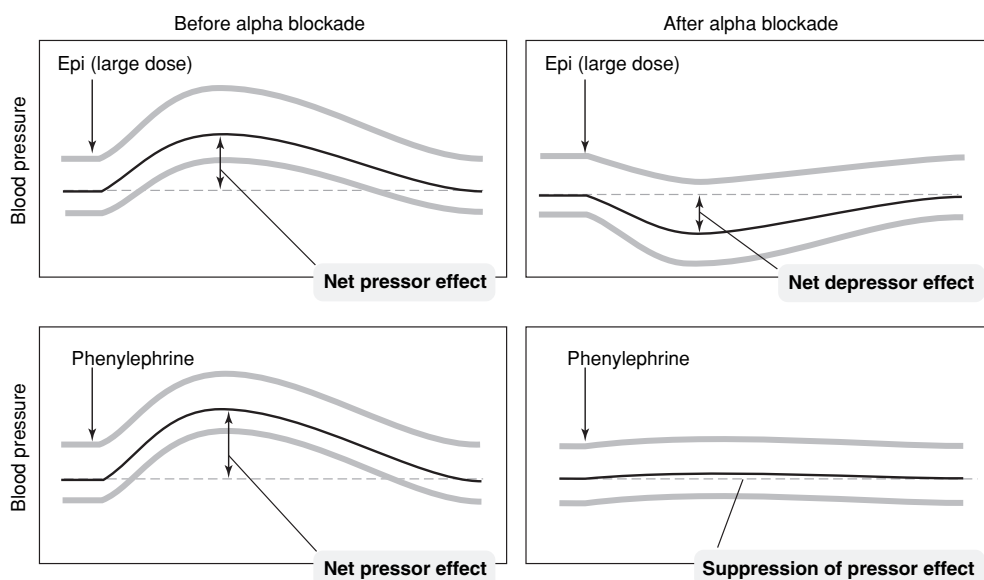
Drug	Mechanism/selectivity	Applications
<b>Catecholamines</b>		
Epinephrine	$\alpha_1, \alpha_2, \beta_1, \beta_2$ , low doses selective for $\beta_1$	Anaphylaxis, glaucoma (open angle), asthma, hypotension
NE	$\alpha_1, \alpha_2 > \beta_1$	Hypotension (but ↓ renal perfusion)
Isoproterenol	$\beta_1 = \beta_2$	AV block (rare)
Dopamine	$D_1 = D_2 > \beta > \alpha$	Shock (↑ renal perfusion), heart failure
Dobutamine	$\beta_1 > \beta_2$	Shock, heart failure cardiac stress testing
<b>Other</b>		
Amphetamine	Indirect general agonist, releases stored catecholamines	Narcolepsy, obesity, attention deficit disorder
Ephedrine	Indirect general agonist, releases stored catecholamines	Nasal decongestion, urinary incontinence, hypotension
Phenylephrine	$\alpha_1 > \alpha_2$	Pupil dilator, vasoconstriction, nasal decongestion
Albuterol, terbutaline	$\beta_2 > \beta_1$	Asthma
Cocaine	Indirect general agonist, uptake inhibitor	Causes vasoconstriction and local anesthesia
Clonidine, $\alpha$ -methyl dopa	Centrally acting $\alpha$ -agonist, ↓ central adrenergic outflow	Hypertension, especially with renal disease (no ↓ in blood flow to kidney)



(Adapted, with permission, from Katzung BG, Trevor AJ. *Pharmacology: Examination & Board Review*, 5th ed. Stamford, CT: Appleton & Lange, 1998:72.)

**$\alpha$ -blockers**

Drugs	Application	Toxicity
<b>Nonselective</b>		
Phenoxybenzamine (irreversible) and phentolamine (reversible)	Pheochromocytoma	Orthostatic hypotension, reflex tachycardia
<b><math>\alpha_1</math> selective</b>		
Prazosin, terazosin, doxazosin	Hypertension, urinary retention in BPH	1st-dose orthostatic hypotension, dizziness, headache
<b><math>\alpha_2</math> selective</b>		
Mirtazapine	Depression	Sedation, $\uparrow$ serum cholesterol, $\uparrow$ appetite



(Adapted, with permission, from Katzung BG, Trevor AJ. *Pharmacology: Examination & Board Review*, 5th ed. Stamford, CT: Appleton & Lange, 1998:80.)

Shown above are the effects of an  $\alpha$ -blocker (e.g., phentolamine) on blood pressure responses to epinephrine and phenylephrine. The epinephrine response exhibits reversal of the mean blood pressure change, from a net increase (the  $\alpha$  response) to a net decrease (the  $\beta_2$  response). The response to phenylephrine is suppressed but not reversed because phenylephrine is a "pure"  $\alpha$ -agonist without  $\beta$  action.

► PHARMACOLOGY—AUTONOMIC DRUGS (*continued*)

<b><math>\beta</math>-blockers</b>	Propranolol, metoprolol, atenolol, nadolol, timolol, pindolol, esmolol, labetalol.
<b>Application</b>	<b>Effect</b>
Hypertension	↓ cardiac output, ↓ renin secretion
Angina pectoris	↓ heart rate and contractility, resulting in ↓ $O_2$ consumption
MI	$\beta$ -blockers ↓ mortality
SVT (propranolol, esmolol)	↓ AV conduction velocity
CHF	Slows progression of chronic failure
Glaucoma (timolol)	↓ secretion of aqueous humor
<b>Toxicity</b>	Impotence, exacerbation of asthma, cardiovascular adverse effects (bradycardia, AV block, CHF), CNS adverse effects (sedation, sleep alterations); use with caution in diabetics
<b>Selectivity</b>	Nonselective ( $\beta_1 = \beta_2$ )—propranolol, timolol, nadolol, pindolol (partial agonist), and labetalol (partial agonist)  $\beta_1$ selective ( $\beta_1 > \beta_2$ )—Acebutolol (partial agonist), <b>A BEAM</b> of $\beta_1$ blockers. <b>B</b> etaxolol, <b>E</b> smolol (short acting), <b>A</b> tenolol, <b>M</b> etoprolol

Specific antidotes	Toxin	Antidote/treatment
	1. Acetaminophen	1. N-acetylcysteine
	2. Salicylates	2. Alkalinize urine, dialysis
	3. Anticholinesterases, organophosphates	3. Atropine, pralidoxime
	4. Antimuscarinic, anticholinergic agents	4. Physostigmine salicylate
	5. $\beta$ -blockers	5. Glucagon
	6. Digitalis	6. Stop dig, normalize $K^+$ , lidocaine, anti-dig Fab fragments, $Mg^{2+}$
	7. Iron	7. Deferoxamine
	8. Lead	8. CaEDTA, dimercaprol, succimer, penicillamine
	9. Arsenic, mercury, gold	9. Dimercaprol (BAL), succimer
	10. Copper, arsenic, gold	10. Penicillamine
	11. Cyanide	11. Nitrite, hydroxocobalamin, thiosulfate
	12. Methemoglobin	12. Methylene blue
	13. Carbon monoxide	13. 100% $O_2$ , hyperbaric $O_2$
	14. Methanol, ethylene glycol (antifreeze)	14. Ethanol, dialysis, fomepizole
	15. Opioids	15. Naloxone/naltrexone
	16. Benzodiazepines	16. Flumazenil
	17. TCAs	17. $NaHCO_3$ (nonspecific)
	18. Heparin	18. Protamine
	19. Warfarin	19. Vitamin K, fresh frozen plasma
	20. tPA, streptokinase	20. Aminocaproic acid
<b>Lead poisoning</b>	<p>Lead Lines on gingivae and on epiphyses of long bones on x-ray.</p> <p>Encephalopathy and Erythrocyte basophilic stippling.</p> <p>Abdominal colic and sideroblastic Anemia.</p> <p>Drops—wrist and foot drop. Dimercaprol and EDTA 1st line of treatment. Succimer for kids.</p>	<p><b>LEAD.</b></p> <p>High risk in houses with chipped paint.</p> <p>It “sucks” to be a kid who eats lead.</p>

► PHARMACOLOGY–TOXICITIES AND SIDE EFFECTS (*continued*)**Drug reactions**

Drug reaction by system	Causal agent
<b>Cardiovascular</b>	
Atropine-like side effects	Tricyclics
Cardiac toxicity	Doxorubicin (Adriamycin), daunorubicin
Coronary vasospasm	Cocaine
Cutaneous flushing	Niacin, Ca <sup>2+</sup> channel blockers, adenosine, vancomycin
Torsades des pointes	Class III (sotalol), class IA (quinidine) antiarrhythmics, cisapride
<b>Hematologic</b>	
Agranulocytosis	Clozapine, carbamazepine, colchicine
Aplastic anemia	Chloramphenicol, benzene, NSAIDs
Gray baby syndrome	Chloramphenicol
Hemolysis in G6PD-deficient patients	Sulfonamides, isoniazid (INH), aspirin, ibuprofen, primaquine, nitrofurantoin
Thrombotic complications	OCPs (e.g., estrogens and progestins)
<b>Respiratory</b>	
Cough	ACE inhibitors (losartan—no cough)
Pulmonary fibrosis	Bleomycin, amiodarone, busulfan
<b>GI</b>	
Acute cholestatic hepatitis	Macrolides
Focal to massive hepatic necrosis	Halothane, valproic acid, acetaminophen, <i>Amanita phalloides</i>
Hepatitis	INH
Pseudomembranous colitis	Clindamycin, ampicillin
<b>Reproductive/endocrine</b>	
Adrenocortical insufficiency	Glucocorticoid withdrawal (HPA suppression)
Gynecomastia	Spironolactone, Digitalis, Cimetidine, chronic Alcohol use, estrogens, Ketoconazole (Some Drugs Create Awesome Knockers)
Hot flashes	Tamoxifen
<b>Musculoskeletal/connective tissue</b>	
Gingival hyperplasia	Phenytoin
Osteoporosis	Corticosteroids, heparin
Photosensitivity	Sulfonamides, Amiodarone, Tetracycline ( <b>SAT</b> for a <b>photo</b> )
SLE-like syndrome	Hydralazine, INH, Procainamide, Phenytoin (it's not <b>HIPP</b> to have lupus)
Tendonitis, tendon rupture, and cartilage damage (kids)	Fluoroquinolones
<b>Renal</b>	
Fanconi's syndrome	Expired tetracycline
Interstitial nephritis	Methicillin
Hemorrhagic cystitis	Cyclophosphamide, ifosfamide

**Drug reactions (continued)****Neurologic**

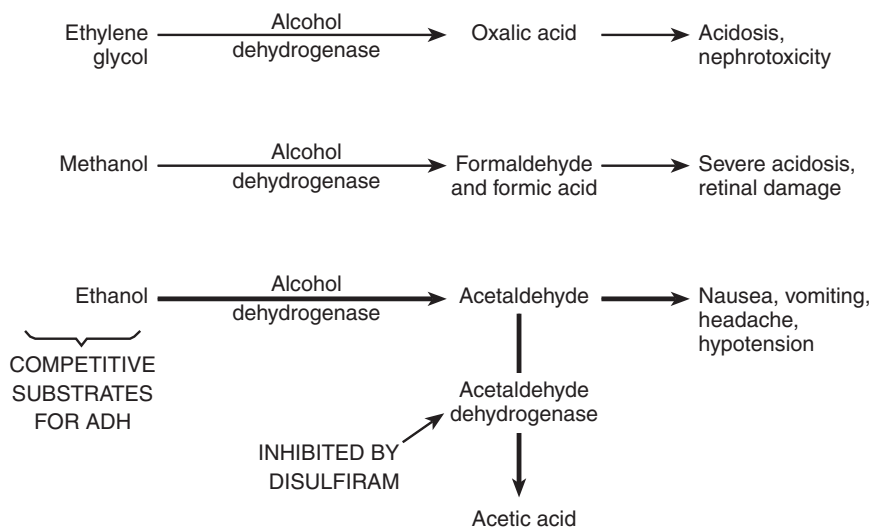
Cinchonism	Quinidine, quinine
Diabetes insipidus	Lithium, demeclocycline
Seizures	Bupropion, imipenem/cilastatin
Tardive dyskinesia	Antipsychotics

**Multiorgan**

Disulfiram-like reaction	Metronidazole, certain cephalosporins, procarbazine, sulfonylureas
Nephrotoxicity/neurotoxicity	Polymyxins
Nephrotoxicity/ototoxicity	Aminoglycosides, loop diuretics, cisplatin

**P-450 interactions**

Inducers	Inhibitors	Inducers:
Quinidine	Isoniazid	Queen Barb takes Phen-phen
Barbiturates	Sulfonamides	and Refuses Greasy Carbs.
Phenytoin	Cimetidine	
Rifampin	Ketoconazole	<b>Inhibitors:</b>
Griseofulvin	Erythromycin	Inhibitors Stop Cyber-Kids
Carbamazepine	Grapefruit juice	from Eating Grapefruit.
St. John's wort		

**Alcohol toxicity**



## ► PHARMACOLOGY—MISCELLANEOUS

**Herbal agents**

Agent	Clinical uses	Toxicities
Echinacea	Common cold	GI distress, dizziness, and headache
Ephedra	As for ephedrine	CNS and cardiovascular stimulation; arrhythmias, stroke, and seizures at high doses
Feverfew	Migraine	GI distress, mouth ulcers, antiplatelet actions
Ginkgo	Intermittent claudication	GI distress, anxiety, insomnia, headache, antiplatelet actions
Kava	Chronic anxiety	GI distress, sedation, ataxia, hepatotoxicity, phototoxicity, dermatotoxicity
Milk thistle	Viral hepatitis	Loose stools
Saw palmetto	Benign prostatic hyperplasia	GI distress, ↓ libido, hypertension
St. John's wort	Mild to moderate depression	GI distress and phototoxicity; serotonin syndrome with SSRIs; inhibits P-450 system
Dehydroepiandrosterone	Symptomatic improvement in females with SLE or AIDS	Androgenization (premenopausal women), estrogenic effects (postmenopausal), feminization (young men)
Melatonin	Jet lag, insomnia	Sedation, suppresses midcycle LH, hypoprolactinemia

(Adapted, with permission, from Katzung BG, Trevor AJ. *USMLE Road Map: Pharmacology*, 1st ed. New York: McGraw-Hill, 2003.)

**Drug name**

Ending	Category	Example
-afil	Erectile dysfunction	Sildenafil
-ane	Inhalational general anesthetic	Halothane
-azepam	Benzodiazepine	Diazepam
-azine	Phenothiazine (neuroleptic, antiemetic)	Chlorpromazine
-azole	Antifungal	Ketoconazole
-barbital	Barbiturate	Phenobarbital
-caine	Local anesthetic	Lidocaine
-cillin	Penicillin	Methicillin
-cycline	Antibiotic, protein synthesis inhibitor	Tetracycline
-ipramine	TCA	Imipramine
-navir	Protease inhibitor	Saquinavir
-olol	β-antagonist	Propranolol
-operidol	Butyrophenone (neuroleptic)	Haloperidol
-oxin	Cardiac glycoside (inotropic agent)	Digoxin
-phylline	Methylxanthine	Theophylline
-pril	ACE inhibitor	Captopril
-terol	β <sub>2</sub> agonist	Albuterol
-tidine	H <sub>2</sub> antagonist	Cimetidine
-triptyline	TCA	Amitriptyline
-tropin	Pituitary hormone	Somatotropin
-zosin	α <sub>1</sub> antagonist	Prazosin

In this section, we have divided the High-Yield Facts into the major **Organ Systems**. Within each Organ System are several subsections, including **Anatomy**, **Physiology**, **Pathology**, and **Pharmacology**. As you progress through each Organ System, refer back to information in the previous subsections to organize these basic science subsections into a “vertical” framework for learning. Below is some general advice for studying the organ systems by these subsections.

### **Anatomy**

Several topics fall under this heading, including embryology, gross anatomy, histology, and neuroanatomy. Do not memorize all the small details; however, do not ignore anatomy altogether. Review what you have already learned and what you wish you had learned. Many questions require two steps. The first step is to identify a structure on anatomic cross section, electron micrograph, or photomicrograph. The second step may require an understanding of the clinical significance of the structure.

When studying, stress clinically important material. For example, be familiar with gross anatomy related to specific diseases (e.g., Pancoast’s tumor, Horner’s syndrome), traumatic injuries (e.g., fractures, sensory and motor nerve deficits), procedures (e.g., lumbar puncture), and common surgeries (e.g., cholecystectomy). There are also many questions on the exam involving x-rays, CT scans, and neuro MRI scans. Many students suggest browsing through a general radiology atlas, pathology atlas, and histology atlas. Focus on learning basic anatomy at key levels in the body (e.g., sagittal brain MRI; axial CT of midthorax, abdomen, and pelvis). Basic neuroanatomy (especially pathways, blood supply, and functional anatomy) also has good yield. Use this as an opportunity to learn associated neuropathology and neurophysiology. Basic embryology (especially congenital malformations) is worth reviewing as well.

### **Physiology**

The portion of the examination dealing with physiology is broad and concept oriented and thus does not lend itself as well to fact-based review. Diagrams are often the best study aids, especially given the increasing number of questions requiring the interpretation of diagrams. Learn to apply basic physiologic relationships in a variety of ways (e.g., Fick equation, clearance equations). You are seldom asked to perform complex calculations. Hormones are the focus of many questions. Learn their sites of production and action as well as their regulatory mechanisms.

A large portion of the physiology tested on the USMLE Step 1 is now clinically relevant and involves understanding physiologic changes associated with pathologic processes (e.g., changes in pulmonary function with COPD). Thus, it is worthwhile to review the physiologic changes that are found with common pathologies of the major organ systems (e.g., heart, lungs, kidneys, GI tract) and endocrine glands.

### **Pathology**

Questions dealing with this discipline are difficult to prepare for because of the sheer volume of material. Review the basic principles and hallmark characteristics of the key diseases. Given the increasingly clinical orientation of Step 1, it is no longer enough to know only the “trigger word” associations of certain diseases (e.g., café-au-lait macules and neurofibromatosis); you must also know the clinical descriptions of these findings.

Given the clinical slant of the USMLE Step 1, it is also important to review the classic presenting signs and symptoms of diseases as well as their associated laboratory findings. Delve into the signs, symptoms, and pathophysiology of the major diseases having a high prevalence in the United States (e.g., alcoholism, diabetes, hypertension, heart failure, ischemic heart disease, infectious disease). Be prepared to think one step beyond the simple diagnosis to treatment or complications.

The examination includes a number of color photomicrographs and photographs of gross specimens that are presented in the setting of a brief clinical history. However, read the question and the choices carefully before looking at the illustration, because the history will help you identify the pathologic process. Flip through an illustrated pathology textbook, color atlases, and appropriate Web sites in order to look at the pictures in the days before the exam. Pay attention to potential clues such as age, sex, ethnicity, occupation, recent activities and exposures, and specialized lab tests.

### **Pharmacology**

Preparation for questions on pharmacology is straightforward. Memorizing all the key drugs and their characteristics (e.g., mechanisms, clinical use, and important side effects) is high yield. Focus on understanding the prototype drugs in each class. Avoid memorizing obscure derivatives. Learn the “classic” and distinguishing toxicities of the major drugs. Do not bother with drug dosages or trade names. Reviewing associated biochemistry, physiology, and microbiology can be useful while studying pharmacology. There is a strong emphasis on ANS, CNS, antimicrobial, and cardiovascular agents as well as on NSAIDs. Much of the material is clinically relevant. Newer drugs on the market are also fair game.



# Cardiovascular

*"As for me, except for an occasional heart attack, I feel as young as I ever did."*

—Robert Benchley

*"Hearts will never be practical until they are made unbreakable."*

—*The Wizard of Oz*

*"As the arteries grow hard, the heart grows soft."*

—H.L. Mencken

*"Nobody has ever measured, not even poets, how much the heart can hold."*

—Zelda Fitzgerald

- ▶ High-Yield Clinical Vignettes
- ▶ Anatomy
- ▶ Physiology
- ▶ Pathology
- ▶ Pharmacology

■ Pregnant woman in 3rd trimester has normal blood pressure when standing and sitting. When supine, blood pressure drops to 90/50.	What is the diagnosis?	Compression of the IVC.
■ 35-year-old man has high blood pressure in his arms and low pressure in his legs.	What is the diagnosis?	Coarctation of the aorta.
■ 5-year-old boy presents with systolic murmur and wide, fixed split S2.	What is the diagnosis?	ASD.
■ During a game, a young football player collapses and dies immediately.	What is the most likely type of cardiac disease?	Hypertrophic cardiomyopathy.
■ Patient has a stroke after incurring multiple long bone fractures in trauma stemming from a motor vehicle accident.	What caused the infarct?	Fat emboli.
■ Elderly woman presents with a headache and jaw pain. Labs show elevated ESR.	What is the diagnosis?	Temporal arteritis.
■ 80-year-old man presents with a systolic crescendo-decrescendo murmur.	What is the most likely cause?	Aortic stenosis.
■ Man starts a medication for hyperlipidemia. He then develops a rash, pruritus, and GI upset.	What drug was it?	Niacin.
■ Patient develops a cough and must discontinue captopril.	What is a good replacement drug, and why doesn't it have the same side effects?	Losartan, an angiotensin II receptor antagonist, does not ↑ bradykinin as captopril does.

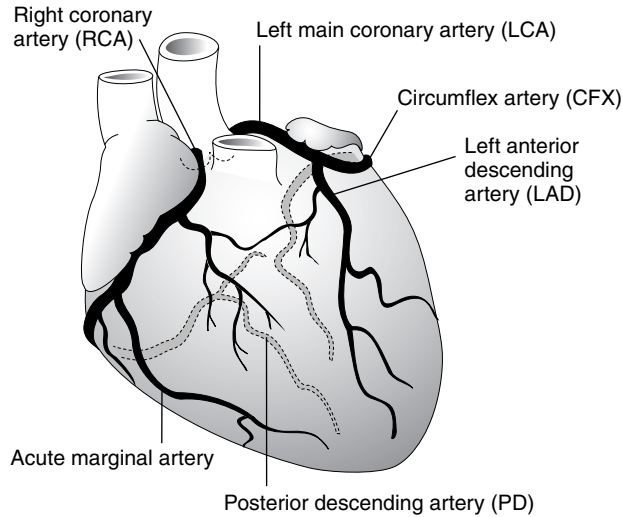
**Carotid sheath**

3 structures inside:

1. Internal jugular Vein (lateral)
2. Common carotid Artery (medial)
3. Vagus Nerve (posterior)

**VAN.**

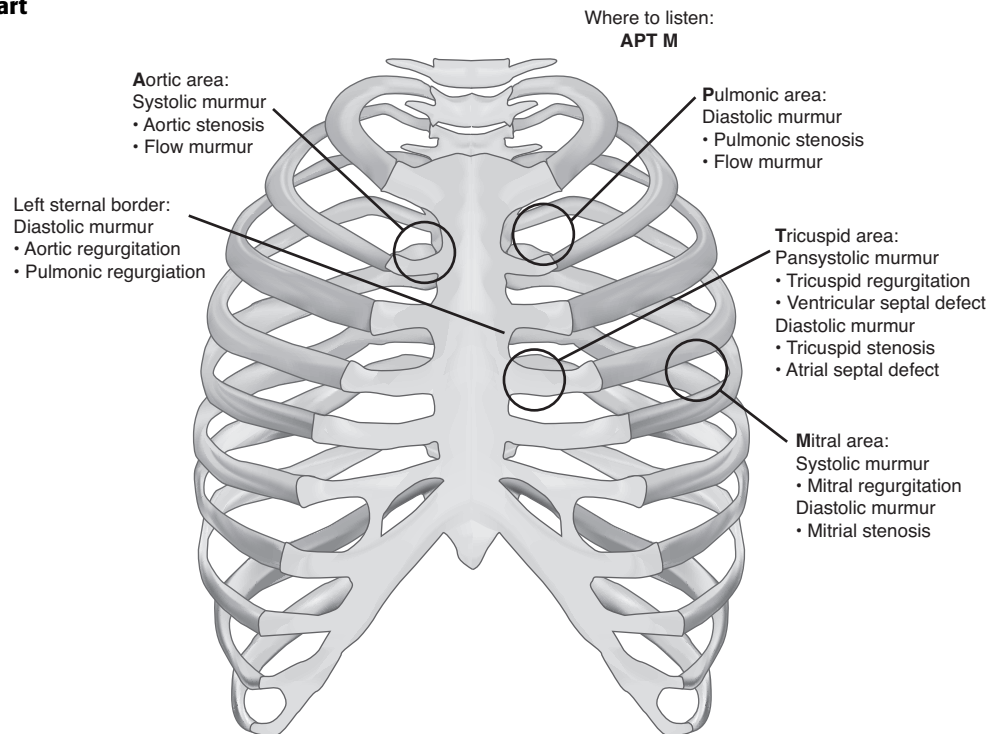
**Coronary artery anatomy**



In the majority of cases, the SA and AV nodes are supplied by the RCA. 80% of the time, the RCA supplies the inferior portion of the left ventricle via the PD artery (= right dominant). Coronary artery occlusion occurs most commonly in the LAD, which supplies the anterior interventricular septum. Coronary arteries fill during diastole. The most posterior part of the heart is the left atrium; enlargement can cause dysphagia.

(Adapted, with permission, from Ganong WF. *Review of Medical Physiology*, 19th ed. Stamford, CT: Appleton & Lange, 1999:592.)

**Auscultation of the heart**



**Cardiac output (CO)**

Cardiac output (CO) = (stroke volume) × (heart rate).  
Fick principle:

$$CO = \frac{\text{rate of O}_2 \text{ consumption}}{\text{arterial O}_2 \text{ content} - \text{venous O}_2 \text{ content}}$$

$$\text{Mean arterial pressure} = \left( \frac{\text{cardiac output}}{\text{output}} \right) \times \left( \frac{\text{total peripheral resistance}}{\text{resistance}} \right)$$

MAP =  $\frac{2}{3}$  diastolic pressure +  $\frac{1}{3}$  systolic pressure.

Pulse pressure = systolic – diastolic.

Pulse pressure ≈ stroke volume.

$$SV = \frac{CO}{HR} = EDV - ESV$$

During exercise, CO ↑ initially as a result of an ↑ in SV. After prolonged exercise, CO ↑ as a result of an ↑ in HR.

If HR is too high, diastolic filling is incomplete and CO ↓ (e.g., ventricular tachycardia).

**Cardiac output variables**

Stroke Volume affected by Contractility, Afterload, and Preload. ↑ SV when ↑ preload, ↓ afterload, or ↑ contractility.

Contractility (and SV) ↑ with:

1. Catecholamines (↑ activity of Ca<sup>2+</sup> pump in sarcoplasmic reticulum)
2. ↑ intracellular calcium
3. ↓ extracellular sodium
4. Digitalis (↑ intracellular Na<sup>+</sup>, resulting in ↑ Ca<sup>2+</sup>)

Contractility (and SV) ↓ with:

1. β<sub>1</sub> blockade
2. Heart failure
3. Acidosis
4. Hypoxia/hypercapnea
5. Ca<sup>2+</sup> channel blockers

**SV CAP.**

SV ↑ in anxiety, exercise, and pregnancy.

A failing heart has ↓ SV.

Myocardial O<sub>2</sub> demand is ↑ by:

1. ↑ afterload (∞ diastolic BP)
2. ↑ contractility
3. ↑ heart rate
4. ↑ heart size (↑ wall tension)

**Preload and afterload**

Preload = ventricular EDV.

Afterload = diastolic arterial pressure (proportional to peripheral resistance).

Venous dilators (e.g., nitroglycerin) ↓ preload.

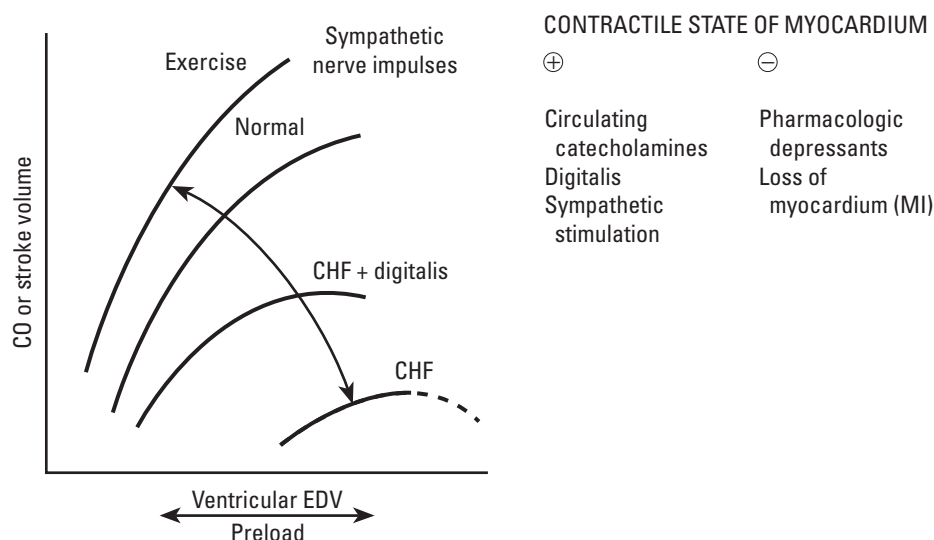
Vasodilators (e.g., hydralazine) ↓ afterload.

Preload ↑ with exercise (slightly), ↑ blood volume (overtransfusion), and excitement (sympathetics).  
Preload pumps up the heart.



**Starling curve**

Force of contraction is proportional to initial length of cardiac muscle fiber (preload).

**Ejection fraction (EF)**

$$EF = \frac{SV}{EDV} = \frac{EDV - ESV}{EDV}$$

EF is an index of ventricular contractility.

EF is normally  $\geq 55\%$ .

**Resistance, pressure, flow**

$$\Delta P = Q \times R$$

Similar to Ohm's law:  $\Delta V = IR$ .

$$\text{Resistance} = \frac{\text{driving pressure } (\Delta P)}{\text{flow } (Q)} = \frac{8\eta \text{ (viscosity)} \times \text{length}}{\pi r^4}$$

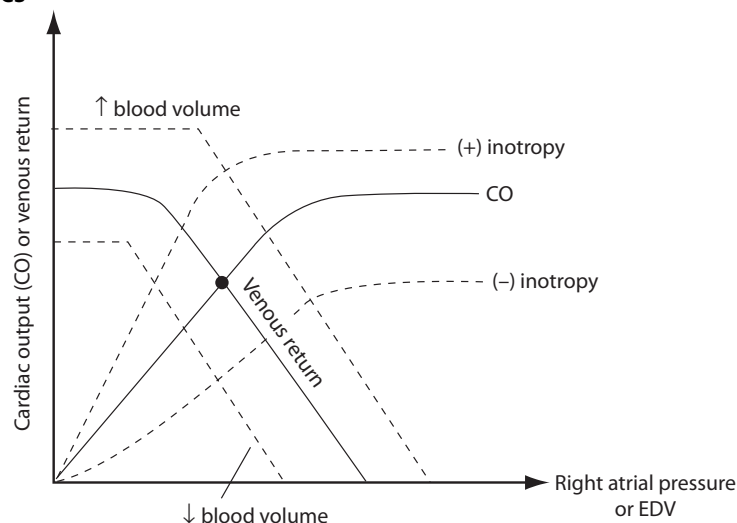
Viscosity depends mostly on hematocrit.

Viscosity  $\uparrow$  in:

1. Polycythemia
2. Hyperproteinemic states (e.g., multiple myeloma)
3. Hereditary spherocytosis

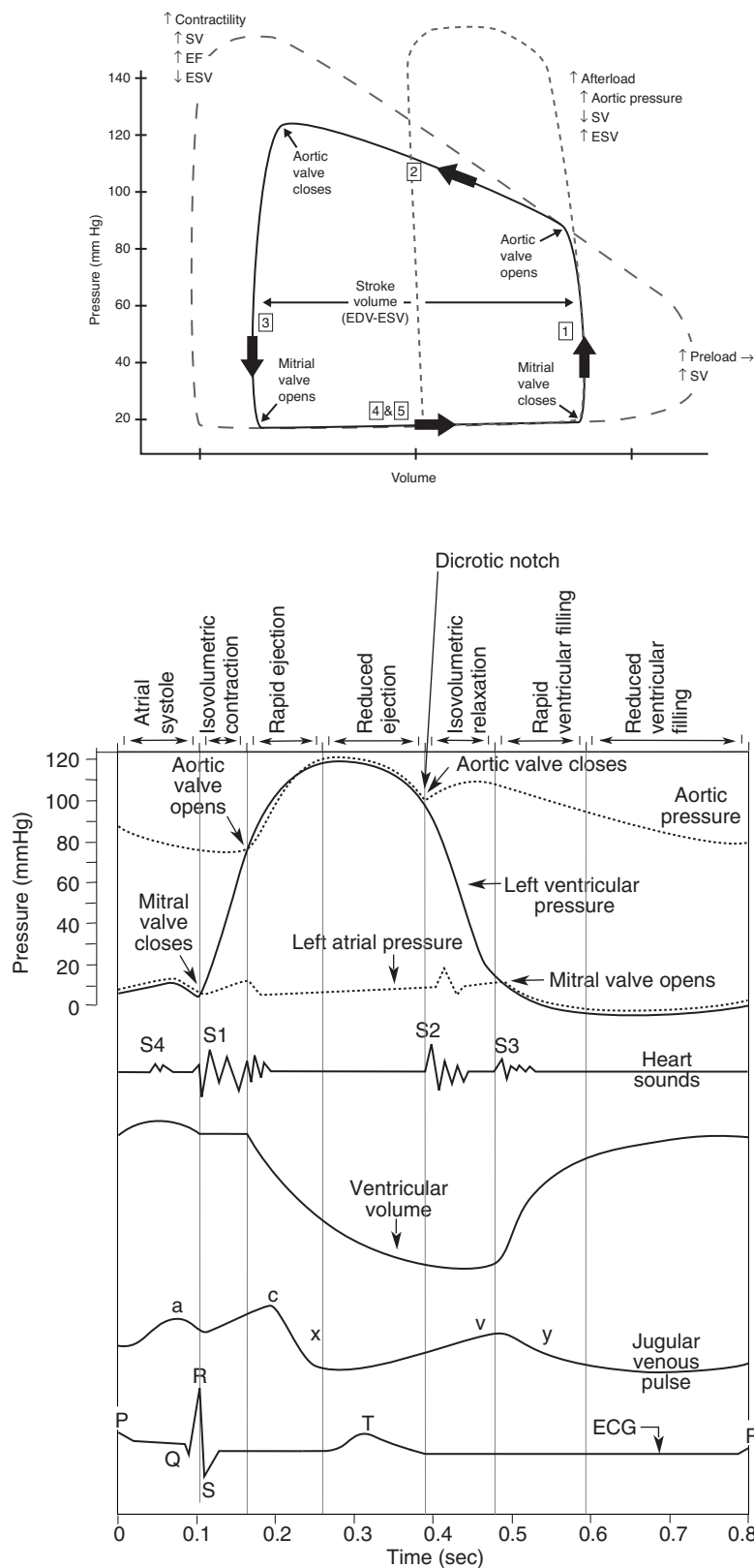
Resistance is directly proportional to viscosity and inversely proportional to the radius to the 4th power.

Arterioles account for most of total peripheral resistance  $\rightarrow$  regulate capillary flow.

**Cardiac and vascular function curves**

## ► CARDIOVASCULAR—PHYSIOLOGY (continued)

## Cardiac cycle



## Phases—left ventricle:

1. Isovolumetric contraction—period between mitral valve closure and aortic valve opening; period of highest  $O_2$  consumption
2. Systolic ejection—period between aortic valve opening and closing
3. Isovolumetric relaxation—period between aortic valve closing and mitral valve opening
4. Rapid filling—period just after mitral valve opening
5. Slow filling—period just before mitral valve closure

## Sounds:

- S1—mitral and tricuspid valve closure.  
 S2—aortic and pulmonary valve closure.  
 S3—at end of rapid ventricular filling.  
 S4—high atrial pressure/stiff ventricle.

S3 is associated with dilated CHF.

S4 (“atrial kick”) is associated with a hypertrophic ventricle.

a wave—atrial contraction.

c wave—RV contraction (tricuspid valve bulging into atrium).

v wave—↑ atrial pressure due to filling against closed tricuspid valve.

S2 splitting: aortic valve closes before pulmonic; inspiration ↑ this difference.

## Normal:

Expiration		
	S <sub>1</sub>	A <sub>2</sub> P <sub>2</sub>
Inspiration		

Wide splitting (associated with pulmonic stenosis):

Expiration		
	S <sub>1</sub>	A <sub>2</sub> P <sub>2</sub>
Inspiration		

Fixed splitting (associated with ASD):

Expiration		
	S <sub>1</sub>	A <sub>2</sub> P <sub>2</sub>
Inspiration		

Paradoxical splitting (associated with aortic stenosis):

Expiration		
	S <sub>1</sub>	P <sub>2</sub> A <sub>2</sub>
Inspiration		

(Adapted, with permission, from Ganong WF. *Review of Medical Physiology*, 22nd ed. McGraw-Hill, 2005.)

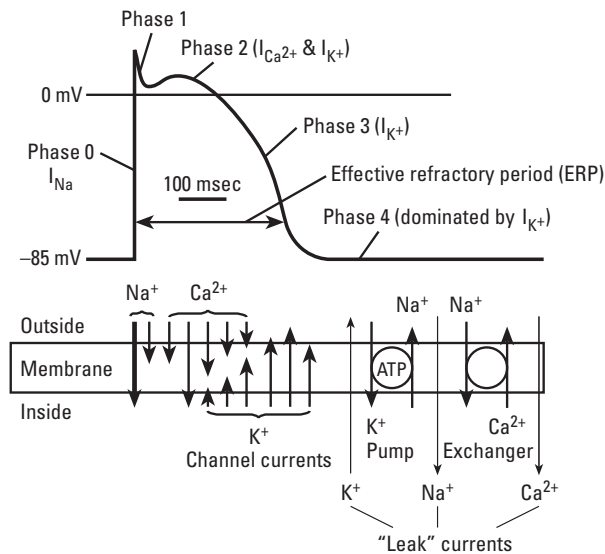
## Cardiac myocyte physiology

Cardiac muscle contraction is dependent on extracellular calcium, which enters the cells during plateau of action potential and stimulates calcium release from the cardiac muscle sarcoplasmic reticulum (calcium-induced calcium release).

In contrast to skeletal muscle:

1. Cardiac muscle action potential has a plateau, which is due to  $\text{Ca}^{2+}$  influx
2. Cardiac nodal cells spontaneously depolarize, resulting in automaticity
3. Cardiac myocytes are electrically coupled to each other by gap junctions

## Myocardial action potential



Occurs in atrial and ventricular myocytes and Purkinje fibers.

**Phase 0** = rapid upstroke—voltage-gated  $\text{Na}^+$  channels open.

**Phase 1** = initial repolarization—inactivation of voltage-gated  $\text{Na}^+$  channels. Voltage-gated  $\text{K}^+$  channels begin to open.

**Phase 2** = plateau— $\text{Ca}^{2+}$  influx through voltage-gated  $\text{Ca}^{2+}$  channels balances  $\text{K}^+$  efflux.  $\text{Ca}^{2+}$  influx triggers  $\text{Ca}^{2+}$  release from sarcoplasmic reticulum and myocyte contraction.

**Phase 3** = rapid repolarization—massive  $\text{K}^+$  efflux due to opening of voltage-gated slow  $\text{K}^+$  channels and closure of voltage-gated  $\text{Ca}^{2+}$  channels.

**Phase 4** = resting potential—high  $\text{K}^+$  permeability through  $\text{K}^+$  channels.

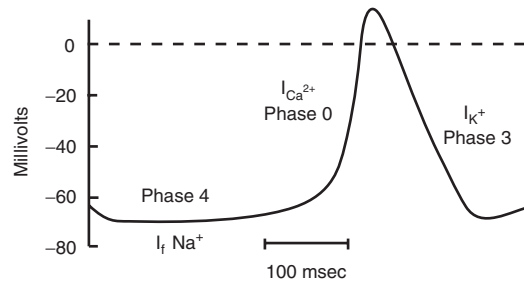
**Pacemaker action potential**

Occurs in the SA and AV nodes. Key differences from the ventricular action potential include:

**Phase 0** = upstroke—opening of voltage-gated  $\text{Ca}^{2+}$  channels. These cells lack fast voltage-gated  $\text{Na}^+$  channels. Results in a slow conduction velocity that is used by the AV node to prolong transmission from the atria to ventricles.

**Phase 2** = plateau is absent.

**Phase 4** = slow diastolic depolarization—membrane potential spontaneously depolarizes as  $\text{Na}^+$  conductance  $\uparrow$  ( $I_f$  different from  $I_{\text{Na}}$  above). Accounts for automaticity of SA and AV nodes. The slope of phase 4 in the SA node determines heart rate. ACh  $\downarrow$  the rate of diastolic depolarization and  $\downarrow$  heart rate, while catecholamines  $\uparrow$  depolarization and  $\uparrow$  heart rate.



(Adapted, with permission, from Ganong WF et al. *Review of Medical Physiology*, 22nd ed. New York: McGraw-Hill, 2005.)

## Electrocardiogram

P wave—atrial depolarization.

PR segment—conduction delay through AV node (normally < 200 msec).

QRS complex—ventricular depolarization (normally < 120 msec).

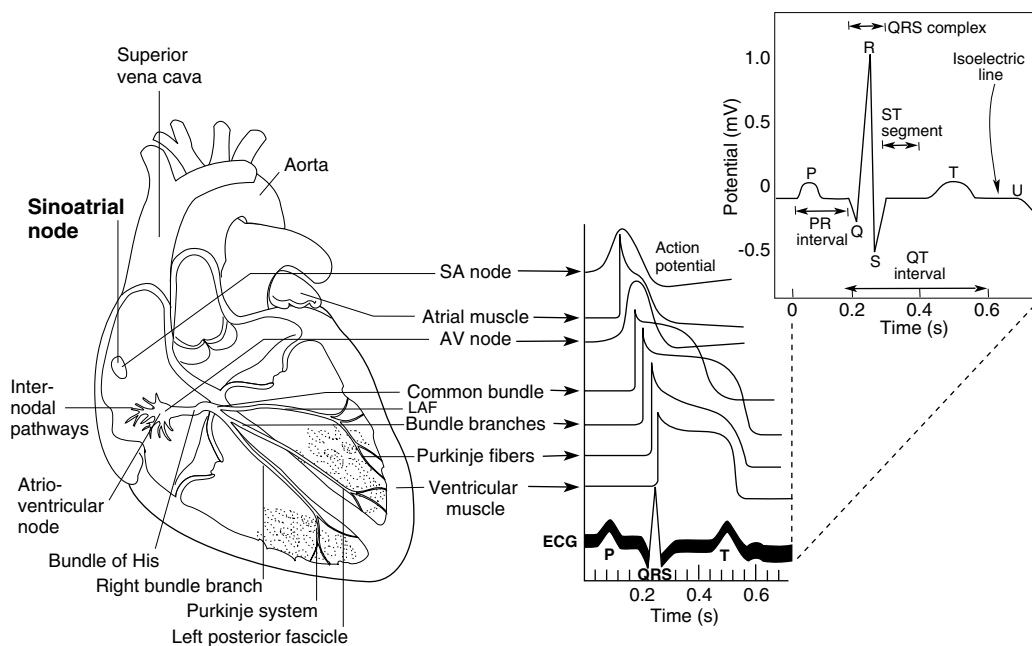
QT interval—mechanical contraction of the ventricles.

T wave—ventricular repolarization.

Atrial repolarization is masked by QRS complex.

ST segment—isolectric, ventricles depolarized.

U wave—caused by hypokalemia.



SA node "pacemaker" inherent dominance with slow phase of upstroke  
 AV node - 100-msec delay - atrioventricular delay

(Adapted, with permission, from Ganong WF. *Review of Medical Physiology*, 22nd ed. New York: McGraw-Hill, 2005:548, 550.)

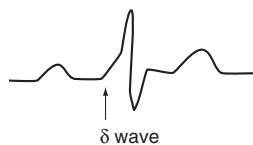
## Torsades des pointes

Ventricular tachycardia characterized by shifting sinusoidal waveforms on ECG.

Can progress to V-fib. Anything that prolongs the QT interval can predispose to torsades des pointes.

## Wolff-Parkinson-White syndrome

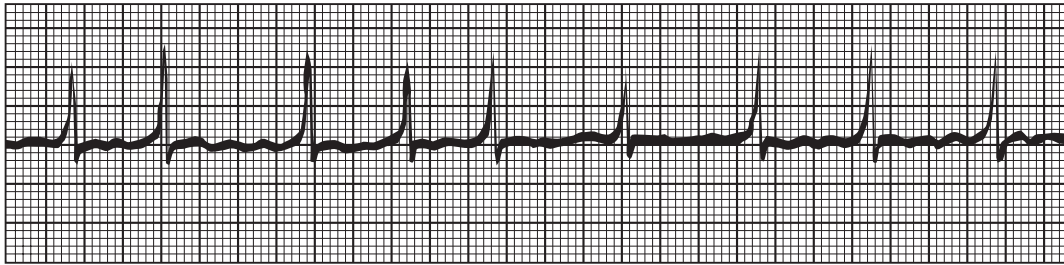
Accessory conduction pathway from atria to ventricle (bundle of Kent), bypassing AV node. As a result, ventricles begin to partially depolarize earlier, giving rise to characteristic delta wave on ECG. May result in reentry current leading to supraventricular tachycardia.



### ECG tracings

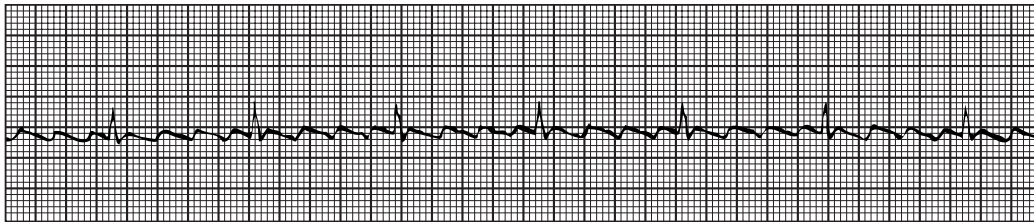
#### Atrial fibrillation

Chaotic and erratic baseline (irregularly irregular) with no discrete P waves in between irregularly spaced QRS complexes.



#### Atrial flutter

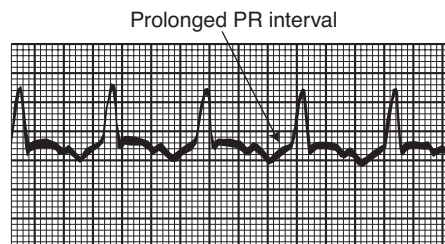
A rapid succession of identical, back-to-back atrial depolarization waves. The identical appearance accounts for the “sawtooth” appearance of the flutter waves.



#### AV block

##### 1st degree

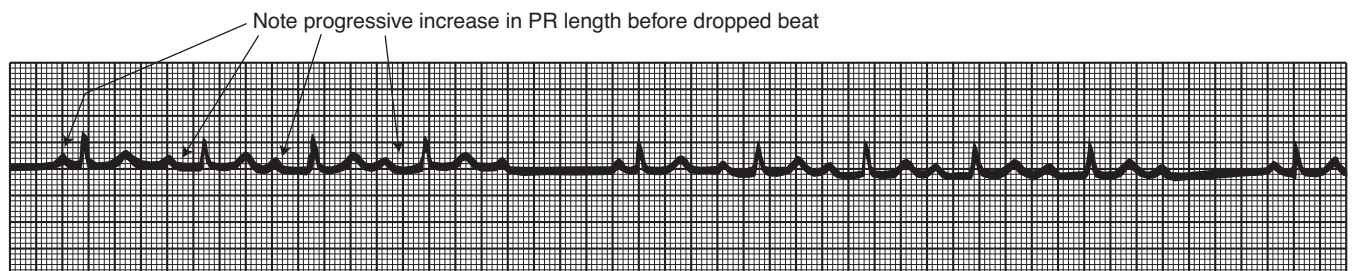
The PR interval is prolonged ( $> 200$  msec). Asymptomatic.



##### 2nd degree

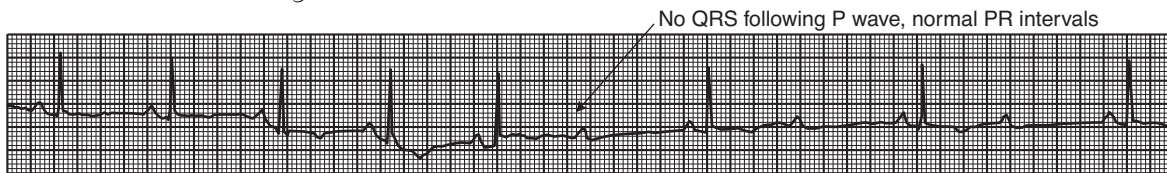
##### Mobitz type I (Wenckebach)

Progressive lengthening of the PR interval until a beat is “dropped” (a P wave not followed by a QRS complex). Usually asymptomatic.

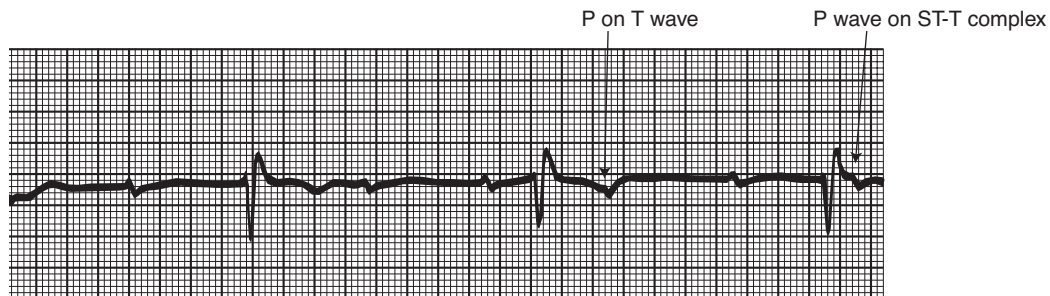


## ECG tracings (continued)

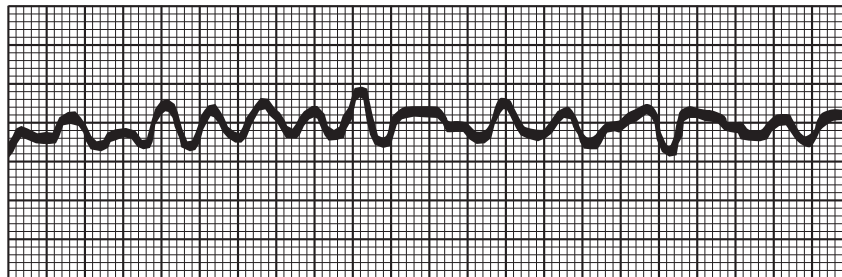
**Mobitz type II**      Dropped beats that are not preceded by a change in the length of the PR interval (as in type I). These abrupt, nonconducted P waves result in a pathologic condition. It is often found as 2:1 block, where there are 2 P waves to 1 QRS response. May progress to 3rd-degree block.



**3rd degree (complete)**      The atria and ventricles beat independently of each other. Both P waves and QRS complexes are present, although the P waves bear no relation to the QRS complexes. The atrial rate is faster than the ventricular rate. Usually treat with pacemaker.

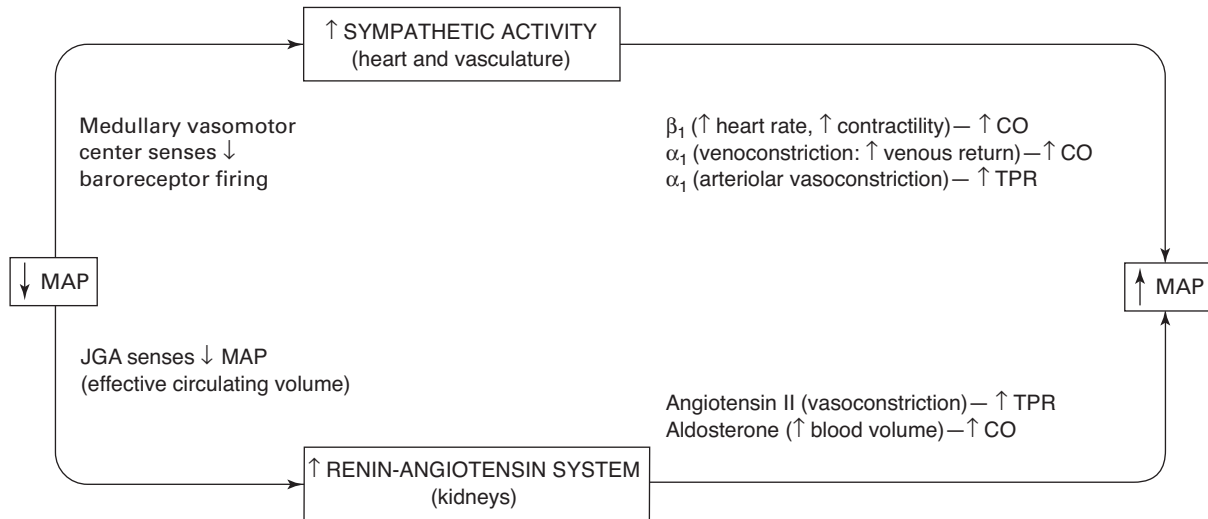


**Ventricular fibrillation**      A completely erratic rhythm with no identifiable waves. Fatal arrhythmia without immediate CPR and defibrillation.

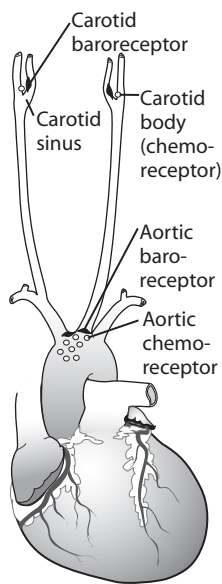


(Adapted, with permission, from Hurst JW. *Introduction to Electrocardiography*. New York: McGraw-Hill, 2001.)

## Control of mean arterial pressure



## Baroreceptors and chemoreceptors



### Receptors:

1. Aortic arch transmits via vagus nerve to medulla (responds only to ↑ BP)
2. Carotid sinus transmits via glossopharyngeal nerve to medulla (responds to ↓ and ↑ in BP).

### Baroreceptors:

1. Hypotension: ↓ arterial pressure → ↓ stretch → ↓ afferent baroreceptor firing → ↑ efferent sympathetic firing and ↓ efferent parasympathetic stimulation → vasoconstriction, ↑ HR, ↑ contractility, ↑ BP. Important in the response to severe hemorrhage.
2. Carotid massage: ↑ pressure on carotid artery → ↑ stretch → ↓ HR.

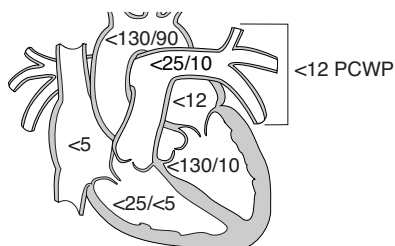
### Chemoreceptors:

1. Peripheral: Carotid and aortic bodies respond to ↓ PO<sub>2</sub> (< 60 mmHg), ↑ PCO<sub>2</sub>, and ↓ pH of blood.
2. Central: Respond to changes in pH and PCO<sub>2</sub> of brain interstitial fluid, which in turn are influenced by arterial CO<sub>2</sub>. Do not directly respond to PO<sub>2</sub>. Responsible for Cushing reaction, response to cerebral ischemia, response to ↑ intracranial pressure → hypertension (sympathetic response) and bradycardia (parasympathetic response).

## Circulation through organs

Liver	Largest share of systemic cardiac output.
Kidney	Highest blood flow per gram of tissue.
Heart	Large arteriovenous O <sub>2</sub> difference. ↑ O <sub>2</sub> demand is met by ↑ coronary blood flow, not by ↑ extraction of O <sub>2</sub> .



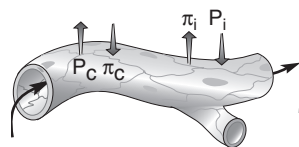
**Normal pressures**

PCWP—pulmonary capillary wedge pressure (in mmHg) is a good approximation of left atrial pressure. Measured with Swan-Ganz catheter.

**Autoregulation**

Organ	Factors determining autoregulation
Heart	Local metabolites: $O_2$ , adenosine, NO
Brain	Local metabolites: $CO_2$ (pH)
Kidneys	Myogenic and tubuloglomerular feedback
Lungs	Hypoxia causes vasoconstriction
Skeletal muscle	Local metabolites: lactate, adenosine, $K^+$
Skin	Sympathetic stimulation most important mechanism—temperature control

Note: the pulmonary vasculature is unique in that hypoxia causes vasoconstriction (in other organs hypoxia causes vasodilation).

**Capillary fluid exchange**

Starling forces determine fluid movement through capillary membranes:

1.  $P_c$  = capillary pressure—moves fluid out of capillary
2.  $P_i$  = interstitial fluid pressure—moves fluid into capillary
3.  $\pi_c$  = plasma colloid osmotic pressure—moves fluid into capillary
4.  $\pi_i$  = interstitial fluid colloid osmotic pressure—moves fluid out of capillary

Thus, net filtration pressure =  $P_{net} = [(P_c - P_i) - (\pi_c - \pi_i)]$ .

$K_f$  = filtration constant (capillary permeability).

Net fluid flow =  $(P_{net}) (K_f)$ .

Edema—excess fluid outflow into interstitium commonly caused by:

1.  $\uparrow$  capillary pressure ( $\uparrow P_c$ ; heart failure)
2.  $\downarrow$  plasma proteins ( $\downarrow \pi_c$ ; nephrotic syndrome, liver failure)
3.  $\uparrow$  capillary permeability ( $\uparrow K_f$ ; toxins, infections, burns)
4.  $\uparrow$  interstitial fluid colloid osmotic pressure ( $\uparrow \pi_i$ ; lymphatic blockage)

**► CARDIOVASCULAR—PATHOLOGY****Congenital heart disease**

Right-to-left shunts (early cyanosis)— “blue babies”	<ol style="list-style-type: none"> <li>1. Tetralogy of Fallot (most common cause of early cyanosis)</li> <li>2. Transposition of great vessels</li> <li>3. Truncus arteriosus</li> </ol>
Left-to-right shunts (late cyanosis)— “blue kids”	<ol style="list-style-type: none"> <li>1. VSD (most common congenital cardiac anomaly)</li> <li>2. ASD (loud S1; wide, fixed split S2)</li> <li>3. PDA (close with indomethacin)</li> </ol>

The 3 T's:

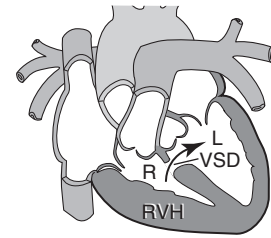
Tetralogy  
Transposition  
Truncus

Children may squat to  
 $\uparrow$  venous return.

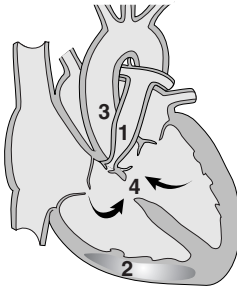
Frequency—VSD > ASD > PDA.  
 $\uparrow$  pulmonary resistance due to arteriolar thickening.  
 $\rightarrow$  progressive pulmonary hypertension; R  $\rightarrow$  L shunt (Eisenmenger's).

**Eisenmenger's syndrome**

Uncorrected VSD, ASD, or PDA leads to progressive pulmonary hypertension. As pulmonary resistance ↑, the shunt reverses from L → R to R → L, which causes late cyanosis (clubbing and polycythemia).



**Tetralogy of Fallot**



1. Pulmonary stenosis (most important determinant for prognosis)
2. RVH
3. Overriding aorta (overrides the VSD)
4. VSD

Early cyanosis is caused by a right-to-left shunt across the VSD. On x-ray, boot-shaped heart due to RVH. Patients suffer “cyanotic spells.” Tetralogy of Fallot is caused by anterosuperior displacement of the infundibular septum.

**PROVe.**

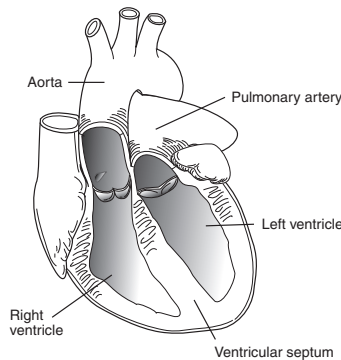
Patient learns to squat to improve symptoms: compression of femoral arteries increases pressure, thereby the R to L shunt.

(Adapted, with permission, from Chandrasoma P. *Concise Pathology*, 3rd ed. Stamford, CT: Appleton & Lange, 1998:345. )

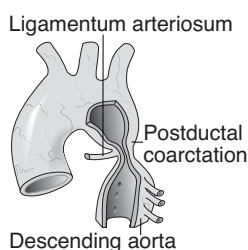
**Transposition of great vessels**

Aorta leaves RV (anterior) and pulmonary trunk leaves LV (posterior) → separation of systemic and pulmonary circulations. Not compatible with life unless a shunt is present to allow adequate mixing of blood (e.g., VSD, PDA, or patent foramen ovale).

Due to failure of the aorticopulmonary septum to spiral. Without surgical correction, most infants die within the first few months of life.



(Adapted, with permission, from Way LW (ed). *Current Surgical Diagnosis and Treatment*, 10th ed. Stamford, CT: Appleton & Lange, 1994:405.)

**Coarctation of aorta**

**Infantile type:** aortic stenosis proximal to insertion of ductus arteriosus (preductal).

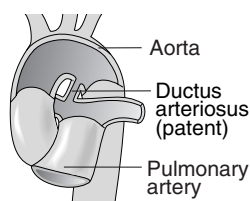
**Adult type:** stenosis is distal to ductus arteriosus (postductal). Associated with notching of the ribs, hypertension in upper extremities, weak pulses in lower extremities.

Associated with Turner's syndrome.

Male-to-female ratio 3:1.  
Check femoral pulses on physical exam.

**IN**fantile: **IN** close to the heart.

**AD**ult: **D**istal to **D**uctus.

**Patent ductus arteriosus**

In fetal period, shunt is right to left (normal). In neonatal period, lung resistance ↓ and shunt becomes left to right with subsequent RVH and failure (abnormal). Associated with a continuous, “machine-like” murmur. Patency is maintained by PGE synthesis and low O<sub>2</sub> tension.

Indomethacin is used to close a PDA. PGE is used to keep a PDA open, which may be necessary to sustain life in conditions such as transposition of the great vessels.

**Congenital cardiac defect associations**

**Disorder**  
22q11 syndromes

Down syndrome  
Congenital rubella  
Turner's syndrome  
Marfan's syndrome  
Offspring of diabetic mother

**Defect**  
Truncus arteriosus, tetralogy of Fallot  
ASD, VSD  
Septal defects, PDA  
Coarctation of aorta  
Aortic insufficiency  
Transposition of great vessels

**Hypertension**

Risk factors

Features

Predisposes to

Defined as BP ≥ 140/90.

↑ age, obesity, diabetes, smoking, genetics, black > white > Asian.

90% of hypertension is 1° (essential) and related to ↑ CO or ↑ TPR; remaining 10% mostly 2° to renal disease. Malignant hypertension is severe and rapidly progressing. Atherosclerosis, stroke, CHF, renal failure, retinopathy, and aortic dissection.

**Hyperlipidemia signs**

Atheromata

Xanthoma

Tendinous xanthoma

Corneal arcus

Plaques in blood vessel walls.

Plaques or nodules composed of lipid-laden histiocytes in the skin, especially the eyelids.

Lipid deposit in tendon, especially Achilles.

Lipid deposit in cornea, nonspecific (arcus senilis).

**Arteriosclerosis**

Mönckeberg

Arteriolosclerosis

Atherosclerosis

Calcification of the arteries, especially radial or ulnar. Usually benign; "pipestem arteries."

Hyaline thickening of small arteries in essential hypertension. Hyperplastic “onion skinning” in malignant hypertension.

Fibrous plaques and atheromas form in intima of arteries.

**Atherosclerosis**

Disease of elastic arteries and large and medium-sized muscular arteries (see Color Image 79).

Risk factors

Smoking, hypertension, diabetes mellitus, hyperlipidemia, family history.

Progression

Fatty streaks → proliferative plaque → complex atheromas.

Complications

Aneurysms, ischemia, infarcts, peripheral vascular disease, thrombus, emboli.

Location

Abdominal aorta > coronary artery > popliteal artery > carotid artery.

Symptoms

Angina, claudication, but can be asymptomatic.

**Ischemic heart disease**

Possible manifestations:

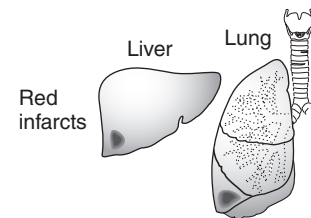
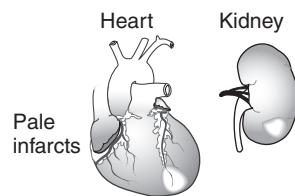
1. **Angina** (CAD narrowing > 75%):
  - a. Stable—mostly 2° to atherosclerosis (retrosternal chest pain with exertion)
  - b. Prinzmetal's variant—occurs at rest 2° to coronary artery spasm
  - c. Unstable/crescendo—thrombosis but no necrosis (worsening chest pain)
2. **Myocardial infarction**—most often acute thrombosis due to coronary artery atherosclerosis. Results in myocyte necrosis.
3. **Sudden cardiac death**—death from cardiac causes within 1 hour of onset of symptoms, most commonly due to a lethal arrhythmia
4. **Chronic ischemic heart disease**—progressive onset of CHF over many years due to chronic ischemic myocardial damage

**Infarcts:  
red vs. pale**

Red (hemorrhagic) infarcts occur in loose tissues with collaterals, such as lungs, intestine, or following reperfusion.

**REd = RE**perfusion.

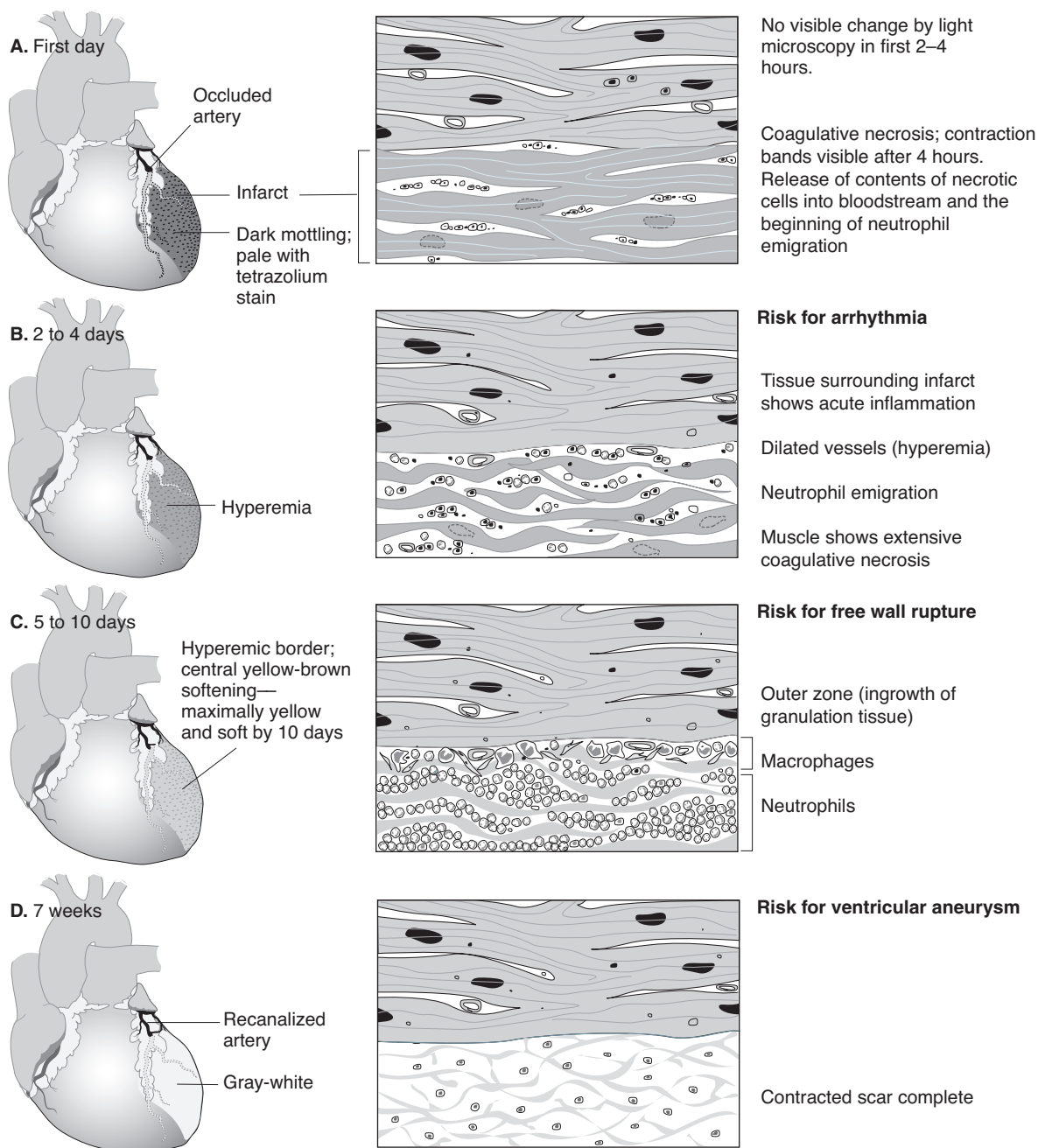
Pale infarcts occur in solid tissues with single blood supply, such as brain, heart, kidney, and spleen.



**Evolution of MI**

Coronary artery occlusion: LAD > RCA > circumflex.

Symptoms: Diaphoresis, nausea, vomiting, severe retrosternal pain, pain in left arm and/or jaw, shortness of breath, fatigue, adrenergic symptoms (see Color Image 80).



(Adapted, with permission, from Chandrasoma P. *Pathology Notes*. Stamford, CT: Appleton & Lange, 1991:244.)

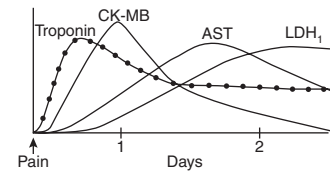
## Diagnosis of MI

In the first 6 hours, ECG is the gold standard. Cardiac troponin I rises after 4 hours and is elevated for 7–10 days; more specific than other protein markers.

CK-MB is predominantly found in myocardium but can also be released from skeletal muscle.

AST is nonspecific and can be found in cardiac, liver, and skeletal muscle cells.

ECG changes can include ST elevation (transmural infarct), ST depression (subendocardial infarct), and pathological Q waves (transmural infarct).



## MI complications

1. Cardiac arrhythmia—important cause of death before reaching hospital; common in first few days
2. LV failure and pulmonary edema
3. Cardiogenic shock (large infarct—high risk of mortality)
4. Rupture of: (1) ventricular free wall, (2) interventricular septum, or (3) papillary muscle (4–10 days post-MI); can lead to cardiac tamponade.
5. Aneurysm formation—↓ CO, risk of arrhythmia, embolus from mural thrombus
6. Fibrinous pericarditis—friction rub (3–5 days post-MI)
7. Dressler's syndrome—autoimmune phenomenon resulting in fibrinous pericarditis (several weeks post-MI)

## Cardiomyopathies

Dilated (congestive) cardiomyopathy

Most common cardiomyopathy (90% of cases). Etiologies include chronic Alcohol abuse, Beriberi, Coxsackie B virus myocarditis, chronic Cocaine use, Chagas' disease, Doxorubicin toxicity, and peripartum cardiomyopathy. Heart dilates and looks like a balloon on chest x-ray.

Systolic dysfunction ensues.

Hypertrophic cardiomyopathy

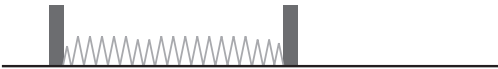
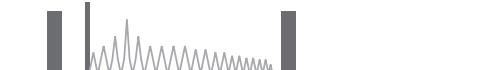
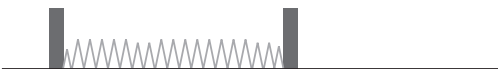
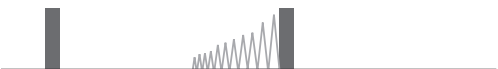
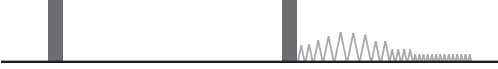

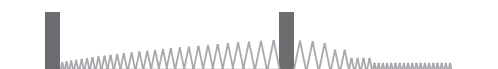
Hypertrophy often asymmetric and involving the intraventricular septum. Normal heart size. 50% of cases are familial, autosomal dominant. Cause of sudden death in young athletes. Findings: loud S4, apical impulses, systolic murmur. Treat with  $\beta$ -blocker.

Diastolic dysfunction ensues.

Restrictive/obliterative cardiomyopathy

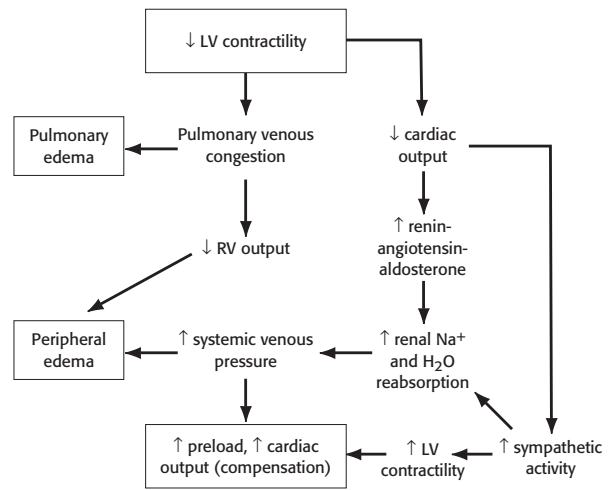
Major causes include sarcoidosis, amyloidosis, postradiation fibrosis, endocardial fibroelastosis, endomyocardial fibrosis (Löffler's), and hemochromatosis (dilated cardiomyopathy can also occur).

**Heart murmurs**

<p>S1                      S2</p> <p>Mitral regurgitation</p> 	<p>Holosystolic high-pitched “blowing murmur.” Loudest at apex.</p>
<p>Aortic stenosis</p> 	<p>Crescendo-decrescendo systolic ejection murmur following ejection click. LV &gt;&gt; aortic pressure during systole. Radiates to carotids/apex. “Pulsus parvus et tardus” pulses weak compared to heart sounds.</p>
<p>VSD</p> 	<p>Holosystolic murmur.</p>
<p>Mitral prolapse</p> 	<p>Late systolic murmur with midsystolic click. Most frequent valvular lesion.</p>
<p>Aortic regurgitation</p> 	<p>Immediate high-pitched “blowing” diastolic murmur. Wide pulse pressure.</p>
<p>Mitral stenosis</p> 	<p>Follows opening snap. Delayed rumbling late diastolic murmur. LA &gt;&gt; LV pressure during diastole. Tricuspid stenosis differs because it gets louder with inspiration.</p>
<p>PDA</p> 	<p>Continuous machine-like murmur. Loudest at time of S2.</p>

**CHF**

Abnormality	Cause
Dyspnea on exertion	Failure of LV output to ↑ during exercise.
Cardiac dilation	Greater ventricular end-diastolic volume.
Pulmonary edema, paroxysmal nocturnal dyspnea	LV failure → ↑ pulmonary venous pressure → pulmonary venous distention and transudation of fluid. Presence of hemosiderin-laden macrophages (“heart failure” cells).
Orthopnea (shortness of breath when supine)	↑ venous return in supine position exacerbates pulmonary vascular congestion.
Hepatomegaly (nutmeg liver)	↑ central venous pressure → ↑ resistance to portal flow. Rarely, leads to “cardiac cirrhosis.”
Ankle, sacral edema	RV failure → ↑ venous pressure → fluid transudation.
Jugular venous distention	R heart failure → ↑ venous pressure.



<b>Embolus types</b>	Fat, Air, Thrombus, Bacteria, Amniotic fluid, Tumor. Fat emboli are associated with long bone fractures and liposuction. Amniotic fluid emboli can lead to DIC, especially postpartum. Pulmonary embolus—chest pain, tachypnea, dyspnea.	An embolus moves like a <b>FAT BAT</b> . Approximately 95% of pulmonary emboli arise from deep leg veins.
<b>Deep venous thrombosis</b>	Predisposed by Virchow’s triad: 1. Stasis 2. Hypercoagulability 3. Endothelial damage	Can lead to pulmonary embolism.
<b>Cardiac tamponade</b>	Compression of heart by fluid (i.e., blood) in pericardium, leading to ↓ CO. Equilibration of pressures in all 4 chambers. Findings: hypotension, ↑ venous pressure (JVD), distant heart sounds, ↑ HR, pulsus paradoxus; ECG shows electrical alternans (beat-to-beat alterations of QRS complex height).	



<b>Bacterial endocarditis</b>	<p>Fever, Roth's spots, <b>Osler's nodes</b> (tender raised lesions on finger or toe pads), (round white spots on retina surrounded by hemorrhage), new <b>murmur</b>, <b>Janeway lesions</b> (small erythematous lesions on palm or sole), anemia, <b>splinter hemorrhages</b> on nail bed. Valvular damage may cause new murmur. Multiple blood cultures necessary for diagnosis (see Color Image 82).</p> <ol style="list-style-type: none"> <li>1. Acute—<i>S. aureus</i> (high virulence). Large vegetations on previously normal valves. Rapid onset.</li> <li>2. Subacute—viridans streptococcus (low virulence). Smaller vegetations on congenitally abnormal or diseased valves. Sequela of dental procedures. More insidious onset.</li> </ol> <p>Endocarditis may also be nonbacterial 2° to metastasis or renal failure (marantic/thrombotic endocarditis).</p>	<p>Mitral valve is most frequently involved. Tricuspid valve endocarditis is associated with IV drug abuse.</p> <p>Complications: chordae rupture, glomerulonephritis, suppurative pericarditis, emboli.</p> <p>Bacteria <b>FROM JANE</b>:</p> <p>Fever Roth's spots Osler's nodes Murmur Janeway lesions Anemia Nail-bed hemorrhage Emboli</p>
<b>Libman-Sacks endocarditis</b>	<p>Vegetations develop on both sides of valve (→ mitral valve stenosis) but do not embolize. Seen in lupus.</p>	<p><b>SLE causes LSE.</b></p>
<b>Rheumatic heart disease</b>	<p>Rheumatic fever is a consequence of pharyngeal infection with group A <math>\beta</math>-hemolytic streptococci. Early deaths due to myocarditis. Late sequelae include rheumatic heart disease, which affects heart valves—mitral &gt; aortic &gt;&gt; tricuspid (high-pressure valves affected most). Associated with Aschoff bodies (granuloma with giant cells), Anitschkow's cells (activated histiocytes), migratory polyarthritis, erythema marginatum, elevated ASO titers.</p> <p>Immune mediated, not direct effect of bacteria (see Color Image 85).</p>	<p><b>FEVERSS:</b></p> <p>Fever Erythema marginatum Valvular damage ESR ↑ Red-hot joints (polyarthritis) Subcutaneous nodules St. Vitus' dance (chorea)</p>
<b>Pericarditis</b> Serous Fibrinous Hemorrhagic	<p>Caused by SLE, rheumatoid arthritis, infection, uremia. Uremia, MI (Dressler's syndrome), rheumatic fever. TB, malignancy (e.g., melanoma).</p> <p>Findings: pericardial pain, friction rub, ECG changes (diffuse ST elevations in all leads), pulsus paradoxus, distant heart sounds.</p> <p>Can resolve without scarring or lead to chronic adhesive or chronic constrictive pericarditis.</p>	

## ► CARDIOVASCULAR–PATHOLOGY (continued)

### Syphilitic heart disease

3° syphilis disrupts the vasa vasora of the aorta with consequent dilation of the aorta and valve ring. Often affects the aortic root and calcification of ascending arch of the aorta.  
May see calcification of the aortic root and ascending aortic arch.

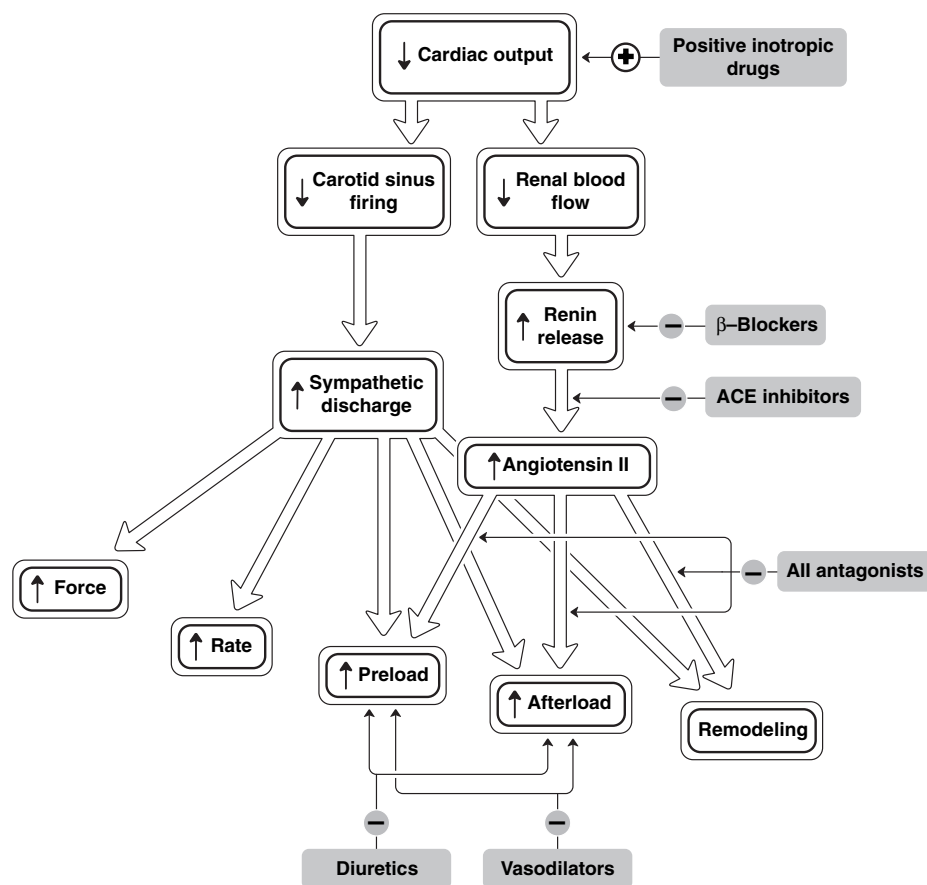
Can result in aneurysm of the ascending aorta or aortic arch and aortic valve incompetence.

### Cardiac tumors

Myxomas are the most common 1° cardiac tumor in adults. 90% occur in the atria (mostly LA). Myxomas are usually described as a “ball-valve” obstruction in the LA. Rhabdomyomas are the most frequent 1° cardiac tumor in children (associated with tuberous sclerosis).  
Metastases most common heart tumor (see Color Image 88).  
Kussmaul's sign: ↑ in systemic venous pressure on inspiration.

## ► CARDIOVASCULAR–PHARMACOLOGY

### Cardiovascular therapy



(Adapted, with permission, from Katzung BG, Trevor AJ. *USMLE Road Map: Pharmacology*, 1st ed. New York: McGraw-Hill, 2003:39.)

**Antihypertensive drugs**

Drug	Adverse effects
<b>Diuretics</b>	
Hydrochlorothiazide	Hypokalemia, slight hyperlipidemia, hyperuricemia, lassitude, hypercalcemia, hyperglycemia
Loop diuretics	Potassium wasting, metabolic alkalosis, hypotension, ototoxicity
<b>Sympathoplegics</b>	
Clonidine	Dry mouth, sedation, severe rebound hypertension
Methyldopa	Sedation, positive Coombs' test
Hexamethonium	Severe orthostatic hypotension, blurred vision, constipation, sexual dysfunction
Reserpine	Sedation, depression, nasal stuffiness, diarrhea
Guanethidine	Orthostatic and exercise hypotension, sexual dysfunction, diarrhea
Prazosin	1st-dose orthostatic hypotension, dizziness, headache
$\beta$ -blockers	Impotence, asthma, cardiovascular effects (bradycardia, CHF, AV block), CNS effects (sedation, sleep alterations)
<b>Vasodilators</b>	
Hydralazine <sup>a</sup>	Nausea, headache, lupus-like syndrome, reflex tachycardia, angina, salt retention
Minoxidil <sup>a</sup>	Hypertrichosis, pericardial effusion, reflex tachycardia, angina, salt retention
Nifedipine, verapamil	Dizziness, flushing, constipation (verapamil), nausea
Nitroprusside	Cyanide toxicity (releases CN)
<b>ACE inhibitors</b>	
Captopril	Hyperkalemia, Cough, Angioedema, Proteinuria, Taste changes, hypotension,
Enalapril	Pregnancy problems (fetal renal damage), Rash, Increased renin, Lower
Fosinopril	angiotensin II
<b>Angiotensin II receptor inhibitors</b>	
Losartan	Fetal renal toxicity, hyperkalemia

<sup>a</sup>Use with  $\beta$ -blockers to prevent reflex tachycardia, diuretic to block salt retention.

**Hydralazine**

Mechanism	$\uparrow$ cGMP $\rightarrow$ smooth muscle relaxation. Vasodilates arterioles > veins; afterload reduction.
Clinical use	Severe hypertension, CHF. First-line for HTN in pregnancy, with methyldopa.
Toxicity	Compensatory tachycardia, fluid retention. Lupus-like syndrome.

**Calcium channel blockers**

	Nifedipine, verapamil, diltiazem.
Mechanism	Block voltage-dependent L-type calcium channels of cardiac and smooth muscle and thereby reduce muscle contractility. Vascular smooth muscle—nifedipine > diltiazem > verapamil. Heart—verapamil > diltiazem > nifedipine.
Clinical use	Hypertension, angina, arrhythmias (not nifedipine), Prinzmetal's angina, Raynaud's.
Toxicity	Cardiac depression, peripheral edema, flushing, dizziness, and constipation.

**Nitroglycerin, isosorbide dinitrate**

Mechanism	Vasodilate by releasing nitric oxide in smooth muscle, causing ↑ in cGMP and smooth muscle relaxation. Dilate veins >> arteries. ↓ preload.
Clinical use	Angina, pulmonary edema. Also used as an aphrodisiac and erection enhancer.
Toxicity	Tachycardia, hypotension, flushing, headache, “Monday disease” in industrial exposure, development of tolerance for the vasodilating action during the work week and loss of tolerance over the weekend, resulting in tachycardia, dizziness, and headache.

**Antianginal therapy**

Goal—reduction of myocardial O<sub>2</sub> consumption (MVO<sub>2</sub>) by decreasing 1 or more of the determinants of MVO<sub>2</sub>: end diastolic volume, blood pressure, heart rate, contractility, ejection time.

Component	Nitrates (affect preload)	β-blockers (affect afterload)	Nitrates + β-blockers
End diastolic volume	↓	↑	No effect or ↓
Blood pressure	↓	↓	↓
Contractility	↑ (reflex response)	↓	Little/no effect
Heart rate	↑ (reflex response)	↓	↓
Ejection time	↓	↑	Little/no effect
MVO <sub>2</sub>	↓	↓	↓↓

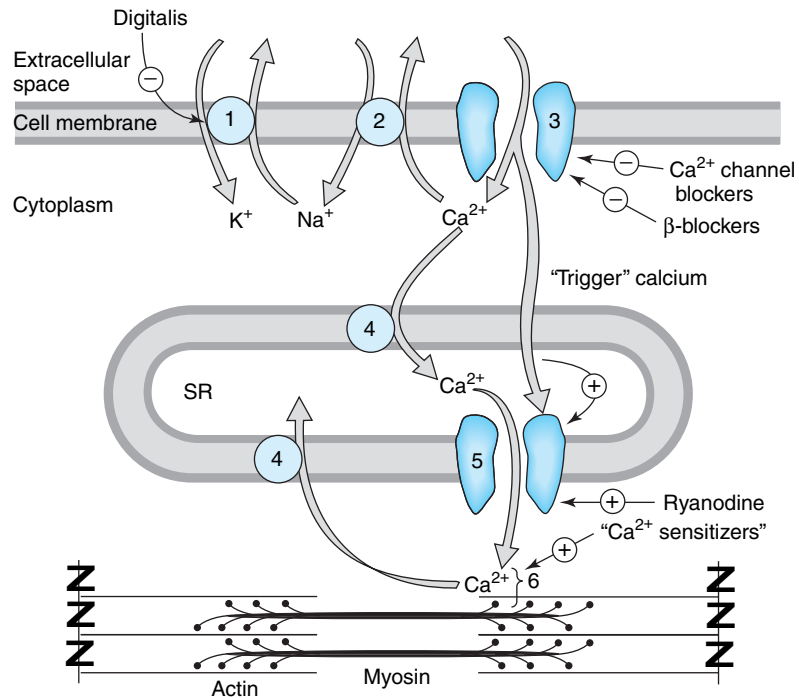
Calcium channel blockers—Nifedipine is similar to Nitrates in effect; verapamil is similar to β-blockers in effect.

## HIGH-YIELD SYSTEMS

## CARDIOVASCULAR



## Cardiac drugs: sites of action



(Adapted, with permission, from Katzung BG. *Basic and Clinical Pharmacology*, 7th ed. Stamford, CT: Appleton & Lange, 1997:198.)

Cardiac sarcomere is shown above with the cellular components involved in excitation-contraction coupling. Factors involved in excitation-contraction coupling are numbered. (1) Na<sup>+</sup>/K<sup>+</sup> ATPase; (2) Na<sup>+</sup>-Ca<sup>2+</sup> exchanger; (3) voltage-gated calcium channel; (4) calcium pump in the wall of the sarcoplasmic reticulum (SR); (5) calcium release channel in the SR; (6) site of calcium interaction with troponin-tropomyosin system.

<b>Cardiac glycosides</b>	Digoxin—75% bioavailability, 20–40% protein bound, $t_{1/2}$ = 40 hours, urinary excretion.
Mechanism	Direct inhibition of Na <sup>+</sup> /K <sup>+</sup> ATPase leads to indirect inhibition of Na <sup>+</sup> /Ca <sup>2+</sup> exchanger/antiport. $\uparrow [Ca^{2+}]_i \rightarrow +$ inotropy.
Clinical use	CHF ( $\uparrow$ contractility); atrial fibrillation ( $\downarrow$ conduction at AV node and depression of SA node).
Toxicity	May cause $\uparrow$ PR, $\downarrow$ QT, scooping of ST segment, T-wave inversion of ECG. Also $\uparrow$ parasympathetic activity: nausea, vomiting, diarrhea, blurry yellow vision (think Van Gogh). Arrhythmia. Toxicities of digoxin are $\uparrow$ by renal failure ( $\downarrow$ excretion), hypokalemia (potentiates drug's effects), and quinidine ( $\downarrow$ digoxin clearance; displaces digoxin from tissue binding sites).
Antidote	Slowly normalize K <sup>+</sup> , lidocaine, cardiac pacer, anti-dig Fab fragments.

## Antiarrhythmics— Na<sup>+</sup> channel blockers (class I)

Local anesthetics. Slow or block (↓) conduction (especially in depolarized cells).  
↓ slope of phase 4 depolarization and ↑ threshold for firing in abnormal pacemaker cells. Are state dependent (selectively depress tissue that is frequently depolarized, e.g., fast tachycardia).

### Class IA

Quinidine, Amiodarone, Procainamide, **Disopyramide**.

“Queen Amy Proclaims  
Diso’s **pyramid**.”

↑ AP duration, ↑ effective refractory period (ERP),  
↑ QT interval. Affect both atrial and ventricular  
arrhythmias especially reentrant and ectopic  
supraventricular and ventricular tachycardia.

Toxicity: quinidine (cinchonism—headache, tinnitus;  
thrombocytopenia; torsades de pointes due to ↑  
QT interval); procainamide (reversible SLE-like  
syndrome).

### Class IB

Lidocaine, mexiletine, tocainide. ↓ AP duration.

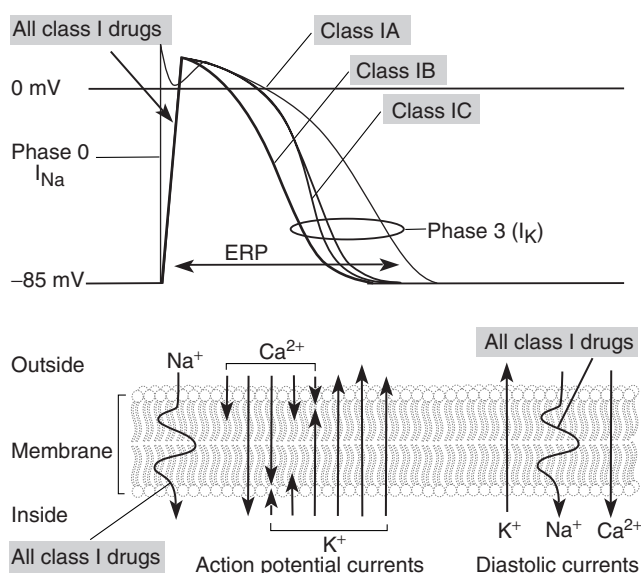
Affect ischemic or depolarized Purkinje and  
ventricular tissue. Useful in acute ventricular  
arrhythmias (especially post-MI) and in  
digitalis-induced arrhythmias.

Toxicity: local anesthetic. CNS stimulation/depression,  
cardiovascular depression.

### Class IC

Flecainide, encainide, propafenone. No effect on  
AP duration. Useful in V-tachs that progress to VF  
and in intractable SVT. Usually used only as last  
resort in refractory tachyarrhythmias.

Toxicity: proarrhythmic, especially post-MI  
(contraindicated). Significantly prolongs  
refractory period in AV node.



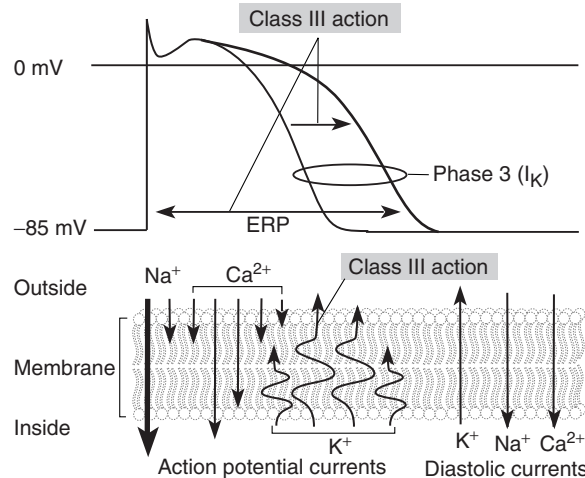
(Adapted, with permission, from Katzung BG, Trevor AJ. *Pharmacology: Examination & Board Review*, 5th ed. Stamford, CT: Appleton & Lange, 1998:118.)

**Antiarrhythmics— $\beta$ -blockers (class II)**

Mechanism	Propranolol, esmolol, metoprolol, atenolol, timolol.  $\downarrow$ cAMP, $\downarrow$ $\text{Ca}^{2+}$ currents. Suppress abnormal pacemakers by $\downarrow$ slope of phase 4. AV node particularly sensitive— $\uparrow$ PR interval. Esmolol very short acting.
Toxicity	Impotence, exacerbation of asthma, cardiovascular effects (bradycardia, AV block, CHF), CNS effects (sedation, sleep alterations). May mask the signs of hypoglycemia. Metoprolol can cause dyslipidemia.

**Antiarrhythmics— $\text{K}^+$  channel blockers (class III)**

Mechanism	Sotalol, ibutilide, bretylium, amiodarone.  $\uparrow$ AP duration, $\uparrow$ ERP. Used when other antiarrhythmics fail. $\uparrow$ QT interval.
Toxicity	Sotalol—torsades de pointes, excessive $\beta$ block; ibutilide—torsades; bretylium—new arrhythmias, hypotension; amiodarone— <b>pulmonary fibrosis</b> , corneal deposits, <b>hepatotoxicity</b> , skin deposits resulting in photodermatitis, neurologic effects, constipation, cardiovascular effects (bradycardia, heart block, CHF), <b>hypothyroidism/hyperthyroidism</b> .  Remember to check <b>PFTs</b> , <b>LFTs</b> , and <b>TFTs</b> when using amiodarone. Amiodarone is safe to use in Wolff-Parkinson-White syndrome.



(Adapted, with permission, from Katzung BG, Trevor AJ. *Pharmacology: Examination & Board Review*, 5th ed. Stamford, CT: Appleton & Lange, 1998:120.)



**Antiarrhythmics—  
Ca<sup>2+</sup> channel  
blockers (class IV)**

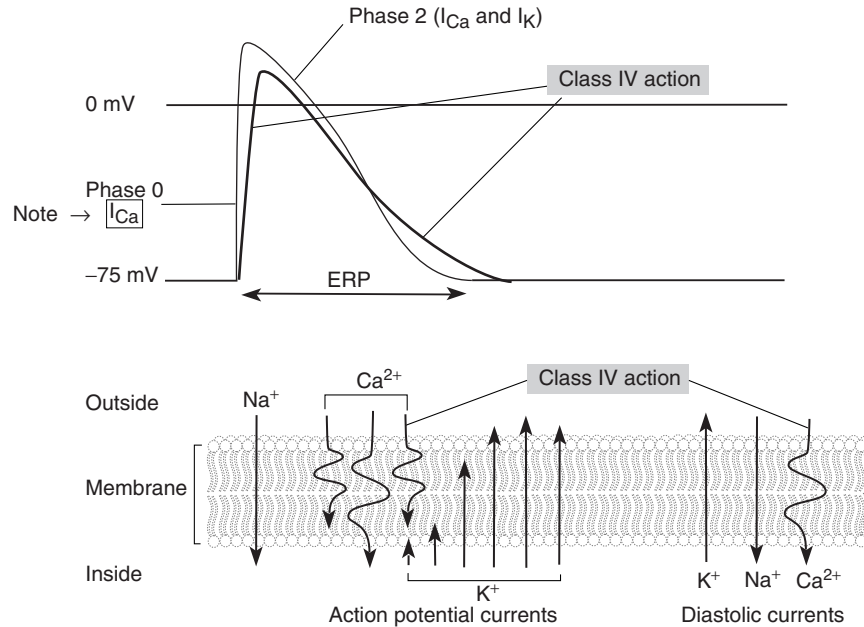
Mechanism

Toxicity

Verapamil, diltiazem.

Primarily affect AV nodal cells. ↓ conduction velocity, ↑ ERP, ↑ PR interval. Used in prevention of nodal arrhythmias (e.g., SVT).

Constipation, flushing, edema, CV effects (CHF, AV block, sinus node depression); torsades de pointes (bepridil).



(Adapted, with permission, from Katzung BG, Trevor AJ. *Pharmacology: Examination & Board Review*, 5th ed. Stamford, CT: Appleton & Lange, 1998:121.)

**Other antiarrhythmics**

Adenosine

K<sup>+</sup>

Mg<sup>+</sup>

Drug of choice in diagnosing/abolishing AV nodal arrhythmias.

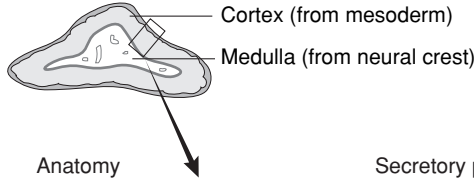

Depresses ectopic pacemakers, especially in digoxin toxicity.

Effective in torsades de pointes and digoxin toxicity.

[illegible]

■ Woman presents with diffuse goiter and hyperthyroidism.	What are the expected values of TSH and thyroid hormones?	Low TSH and high thyroid hormones.
■ 48-year-old female presents with progressive lethargy and extreme sensitivity to cold temperatures.	What is the diagnosis?	Hypothyroidism.
■ Patient with elevated serum cortisol levels undergoes a dexamethasone suppression test. 1 mg of dexamethasone does not ↓ cortisol levels, but 8 mg does.	What is the diagnosis?	Pituitary tumor.
■ 50-year-old man complains of diarrhea. On physical exam, his face is plethoric and a heart murmur is detected.	What is the diagnosis?	Carcinoid syndrome.
■ Woman of short stature presents with shortened 4th and 5th metacarpals.	What endocrine disorder comes to mind?	Albright's hereditary osteodystrophy, or pseudohypoparathyroidism.
■ Nondiabetic patient presents with hypoglycemia but low levels of C peptide.	What is the diagnosis?	Surreptitious insulin injection.
■ Patient's MRI shows filling of sella tursica with cerebrospinal fluid.	What is the most likely clinical presentation?	Normal. Residual pituitary tissue is functional and can compensate (empty sella syndrome).

## Adrenal cortex and medulla

			
Primary regulatory control	Anatomy	Secretory products	
	Capsule		
Renin-angiotensin	→ Zona Glomerulosa	→ Aldosterone	
ACTH, hypothalamic CRH	→ Zona Fasciculata	→ Cortisol, sex hormones	
ACTH, hypothalamic CRH	→ Zona Reticularis	→ Sex hormones (e.g., androgens)	
Preganglionic sympathetic fibers	→ Medulla	→ Catecholamines (Epi, NE)	
	Chromaffin cells →		
<hr/>			
<b>Adrenal gland drainage</b>	Left adrenal → left adrenal vein → left renal vein → IVC. Right adrenal → right adrenal vein → IVC.		
<hr/>			
<b>Pituitary gland</b>	Posterior pituitary (neurohypophysis) → vasopressin and oxytocin, made in the hypothalamus and shipped to pituitary. Derived from neuroectoderm. Anterior pituitary (adenohypophysis) → FSH, LH, ACTH, GH, TSH, melanotropin (MSH), prolactin. Derived from oral ectoderm. $\alpha$ subunit—common subunit to TSH, LH, FSH, and hCG. $\beta$ subunit—determines hormone specificity.	Acidophils—GH, prolactin. <b>B-Flat:</b> Basophils—FSH, LH, ACTH, TSH <b>FLAT PiG:</b> FSH LH ACTH TSH Prolactin GH	
<hr/>			
<b>Endocrine pancreas cell types</b>	Islets of Langerhans are collections of $\alpha$ , $\beta$ , and $\delta$ endocrine cells (most numerous in tail of pancreas). Islets arise from pancreatic buds. $\alpha$ = glucagon (peripheral); $\beta$ = insulin (central); $\delta$ = somatostatin (interspersed).		

GFR corresponds with Salt ( $\text{Na}^+$ ), Sugar (glucocorticoids), and Sex (androgens).

“The deeper you go, the sweeter it gets.”

**Pheochromocytoma**—most common tumor of the adrenal medulla in adults.

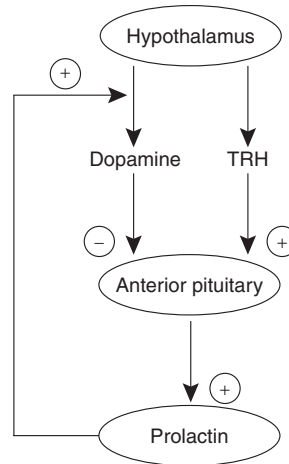
**Neuroblastoma**—most common in children.

Pheochromocytoma causes episodic hypertension; neuroblastoma does not.

**Prolactin regulation**

Prolactin  $\uparrow$  dopamine synthesis and secretion from the hypothalamus. Dopamine subsequently **inhibits** prolactin secretion. Dopamine agonists (e.g., bromocriptine) therefore **inhibit** prolactin secretion, whereas dopamine antagonists (e.g., most antipsychotics) stimulate prolactin secretion. In females, prolactin inhibits GnRH synthesis and release, which inhibits ovulation. Amenorrhea is commonly seen in prolactinomas.

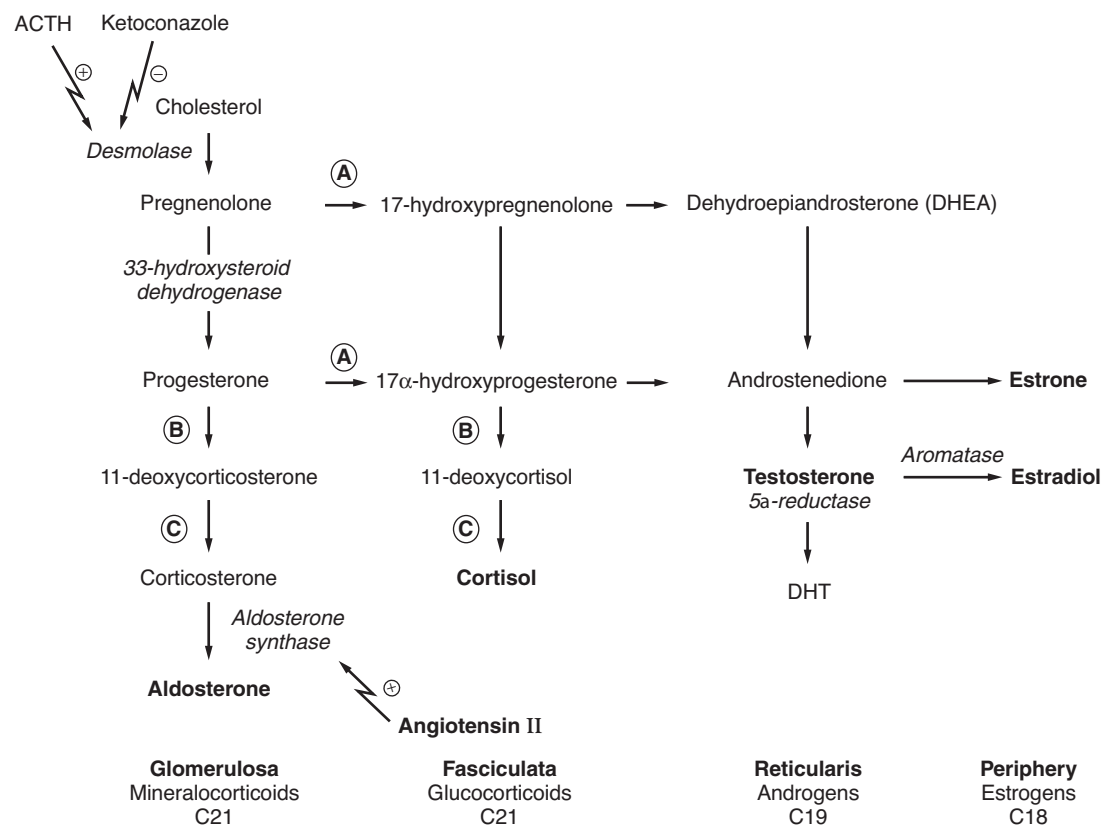
**Prolactin regulation**



**Hypothalamic-pituitary hormone regulation**

TRH —  $\oplus$   $\rightarrow$  TSH, prolactin  
 Dopamine —  $\ominus$   $\rightarrow$  prolactin  
 CRH —  $\oplus$   $\rightarrow$  ACTH  
 GHRH —  $\oplus$   $\rightarrow$  GH  
 Somatostatin —  $\ominus$   $\rightarrow$  GH, TSH  
 GnRH —  $\oplus$   $\rightarrow$  FSH, LH

## Adrenal steroids



Congenital  
bilateral  
adrenal  
hyperplasias

- A = 17α-hydroxylase deficiency.** ↓ sex hormones, ↓ cortisol, ↑ mineralocorticoids. Cx = **HYPER**tension, hypokalemia; phenotypically female but no maturation.
- B = 21β-hydroxylase deficiency.** Most common form. ↓ cortisol (increased ACTH), ↓ mineralocorticoids, ↑ sex hormones. Cx = masculinization, female pseudohermaphroditism, **HYPO**tension, hyponatremia, hyperkalemia, ↑ plasma renin activity, and volume depletion. Salt wasting can lead to hypovolemic shock in the newborn.
- C = 11β-hydroxylase deficiency.** ↓ cortisol, ↓ aldosterone and corticosterone, ↑ sex hormones. Cx = masculinization, **HYPER**tension (11-deoxycorticosterone acts as a weak mineralocorticoid).

## PTH

Source

Chief cells of parathyroid.

Function

1. ↑ bone resorption of calcium and phosphate
2. ↑ kidney reabsorption of calcium in distal convoluted tubule
3. ↓ kidney reabsorption of phosphate
4. ↑ 1,25-(OH)<sub>2</sub> vitamin D (cholecalciferol) production by stimulating kidney 1α-hydroxylase

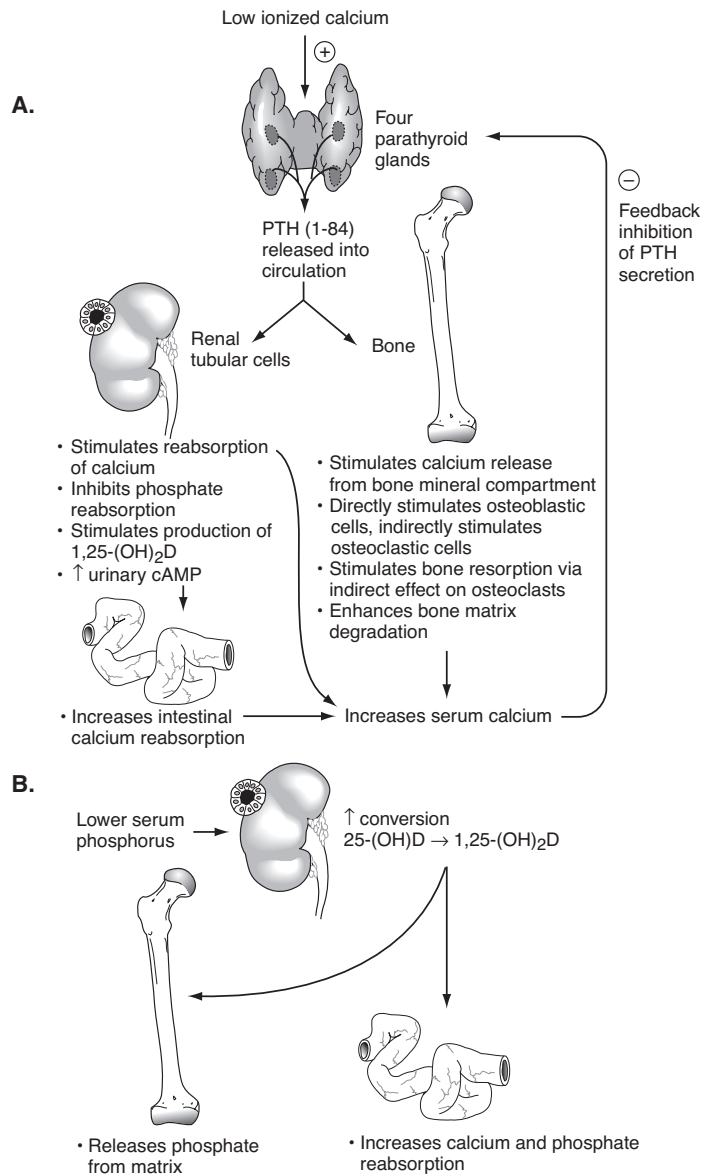
PTH ↑ serum Ca<sup>2+</sup>, ↓ serum (PO<sub>4</sub>)<sup>3-</sup>, ↑ urine (PO<sub>4</sub>)<sup>3-</sup>.

PTH stimulates both osteoclasts and osteoblasts.

**PTH = Phosphate Trashing Hormone.**

Regulation

↓ in free serum Ca<sup>2+</sup> ↑ PTH secretion.



(Adapted, with permission, from Chandrasoma P et al. *Concise Pathology*, 3rd ed. Stamford, CT: Appleton & Lange, 1998.)

Shown above are the main actions of PTH and 1,25-(OH)<sub>2</sub>D in the maintenance of calcium (A) and phosphate (B) homeostasis.

**Vitamin D**

Source	Vitamin D <sub>3</sub> from sun exposure in skin. D <sub>2</sub> from plants. Both converted to 25-OH vitamin D in liver and to 1,25-(OH) <sub>2</sub> vitamin D (active form) in kidney.	If you do not get vitamin D, you get rickets (kids) or osteomalacia (adults). 24,25-(OH) <sub>2</sub> vitamin D is an inactive form of vitamin D.
Function	1. ↑ absorption of dietary calcium 2. ↑ absorption of dietary phosphate 3. ↑ bone resorption of Ca <sup>2+</sup> and (PO <sub>4</sub> ) <sup>3-</sup>	
Regulation	↑ PTH causes ↑ 1,25-(OH) <sub>2</sub> vitamin D production. ↓ [Ca <sup>2+</sup> ] ↑ 1,25-(OH) <sub>2</sub> vitamin D production. ↓ phosphate causes ↑ 1,25-(OH) <sub>2</sub> vitamin D production. 1,25-(OH) <sub>2</sub> vitamin D feedback inhibits its own production.	

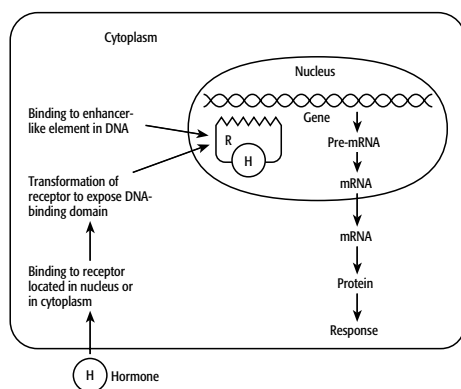
**Calcium, phosphate, and alkaline phosphatase levels**

	Ca <sup>2+</sup>	Phosphate	Alkaline phosphatase
Hyperparathyroidism	↑	↓	↑
Paget's disease of bone	N/↑	N	↑↑↑
Vitamin D intoxication	↑	↑	N/↑
Osteoporosis	N	N	N
Renal insufficiency	↓	↑	N

N = no change.

**Calcitonin**

Source	Parafollicular cells (C cells) of thyroid.	Calcitonin opposes actions of PTH. It is probably not important in normal calcium homeostasis.
Function	↓ bone resorption of calcium.	
Regulation	↑ serum Ca <sup>2+</sup> causes calcitonin secretion.	

**Steroid/thyroid hormone mechanism**

(Adapted, with permission, from Ganong WF. *Review of Medical Physiology*, 22th ed. New York: McGraw-Hill, 2005.)

The need for gene transcription and protein synthesis delays the onset of action of these hormones.

Steroid/thyroid hormones—

**PET CAT:**

Progesterone  
Estrogen  
Testosterone  
Cortisol  
Aldosterone  
Thyroxine and T<sub>3</sub>

Steroid hormones are lipophilic and relatively insoluble in plasma; therefore, they must circulate bound to specific binding globulins, which ↑ solubility and allows for ↑ delivery of steroid to the target organ. ↑ levels of sex hormone-binding globulin (SHBG) lower free testosterone → gynecomastia. ↓ SHBG raises free testosterone → hirsutism.



### Thyroid hormones

( $T_3/T_4$ )

Source

Function

Regulation

Iodine-containing hormones that control the body's metabolic rate.

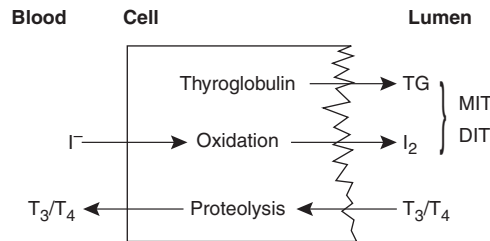
Follicles of thyroid. Most  $T_3$  formed in blood.

1. Bone growth (synergism with GH)
  2. CNS maturation
  3.  $\beta$ -adrenergic effects ( $\uparrow$  CO, HR, SV, contractility)
  4.  $\uparrow$  basal metabolic rate via  $\uparrow$   $Na^+/K^+$  ATPase activity =  $\uparrow$   $O_2$  consumption, RR,  $\uparrow$  body temperature
  5.  $\uparrow$  glycogenolysis, gluconeogenesis, lipolysis
- TRH (hypothalamus) stimulates TSH (pituitary), which stimulates follicular cells. Negative feedback by  $T_3$  to anterior pituitary  $\downarrow$  sensitivity to TRH. TSI, like TSH, stimulates follicular cells (Graves' disease).

$T_3$  functions—4 B's:

- Brain maturation
- Bone growth
- Beta-adrenergic effects
- BMR  $\uparrow$

Thyroxine-binding globulin (TBG) binds most  $T_3/T_4$  in blood; only free hormone is active.  $\downarrow$  TBG in hepatic failure;  $\uparrow$  TBG in pregnancy (estrogen increases TBG).



### Insulin-dependent organs

Skeletal muscle and adipose tissue depend on insulin for  $\uparrow$  glucose uptake (GLUT-4). Brain and RBCs take up glucose independent of insulin levels (GLUT-1).

Brain and RBCs depend on glucose for metabolism under normal circumstances. Brain uses ketone bodies in starvation.

### Cortisol

Source

Function

Regulation

Adrenal fasciculata

1. Anti-inflammatory
2.  $\uparrow$  gluconeogenesis, lipolysis, proteolysis
3.  $\downarrow$  immune function
4. Maintains blood pressure
5.  $\downarrow$  bone formation

CRH (hypothalamus) stimulates ACTH release (pituitary) causing cortisol production in adrenal fasciculata.

Bound to corticosteroid binding globulin (CBG).

Chronic stress induces prolonged secretion.

**Cushing's syndrome**

↑ cortisol due to a variety of causes.

Etiologies include:

1. Cushing's disease (1° pituitary adenoma); ↑ ACTH
2. 1° adrenal (hyperplasia/neoplasia); ↓ ACTH (see Color Image 68)
3. Ectopic ACTH production (e.g., small cell lung cancer); ↑ ACTH
4. Iatrogenic (e.g., chronic steroids); ↓ ACTH

The clinical picture includes hypertension, weight gain, moon facies, truncal obesity, buffalo hump, hyperglycemia (insulin resistance), skin changes (thinning, striae), osteoporosis, amenorrhea, and immune suppression (see Color Image 70).

Dexamethasone suppression test:

Healthy—↓ cortisol after low dose.

ACTH-producing tumor—  
↑ cortisol after low dose;  
↓ cortisol after high dose.

Cortisone-producing tumor—↑ cortisol after low and high dose.

**Hyperaldosteronism**

Primary (Conn's syndrome)

Caused by an aldosterone-secreting tumor, resulting in hypertension, hypokalemia, metabolic alkalosis, and **low** plasma renin.

Treatment includes spironolactone, a K<sup>+</sup>-sparing diuretic that works by acting as an aldosterone antagonist.

Secondary

Due to renal artery stenosis, chronic renal failure, CHF, cirrhosis, or nephrotic syndrome. Kidney perception of low intravascular volume results in an overactive renin-angiotensin system. Therefore, it is associated with **high** plasma renin.

**Addison's disease**

1° deficiency of aldosterone and cortisol due to adrenal atrophy, causing hypotension (hyponatremic volume contraction) and skin hyperpigmentation (due to MSH, a by-product of ↑ ACTH production from POMC). Characterized by **Adrenal Atrophy** and **Absence** of hormone production; involves **All 3** cortical divisions. Distinguish from 2° insufficiency, which has no skin hyperpigmentation (↓ pituitary ACTH production).

**Tumors of the adrenal medulla**

Pheochromocytoma

The most common tumor of the adrenal medulla in adults. Derived from chromaffin cells (arise from neural crest) (see Color Image 69). VMA in urine.

Pheochromocytomas may be associated with neurofibromatosis, MEN types II and III.

Neuroblastoma

The most common tumor of the adrenal medulla in children, but it can occur anywhere along the sympathetic chain. HVA in urine. Less likely to develop hypertension.

**Sheehan's syndrome**

Postpartum hypopituitarism. Caused by infarction of the pituitary gland following severe bleeding and hypoperfusion during delivery. May cause fatigue, anorexia, poor lactation, and loss of pubic and axillary hair.

<b>Pheochromocytoma</b>	<p>Most of these tumors secrete epinephrine, NE, and dopamine. Urinary VMA levels and plasma catecholamines are elevated. Associated with MEN types II and III. Treated with <math>\alpha</math>-antagonists, especially phenoxybenzamine, a nonselective, <b>irreversible</b> <math>\alpha</math>-blocker.</p> <p>Episodic hyperadrenergic symptoms (<b>5 P's</b>):</p> <ul style="list-style-type: none"> <li>Pressure (elevated blood pressure)</li> <li>Pain (headache)</li> <li>Perspiration (tachycardia)</li> <li>Palpitations</li> <li>Pallor</li> </ul>	<p><b>Rule of 10's:</b></p> <ul style="list-style-type: none"> <li>10% malignant</li> <li>10% bilateral</li> <li>10% extra-adrenal</li> <li>10% calcify</li> <li>10% kids</li> <li>10% familial</li> </ul> <p>Symptoms occur in “spells”—relapse and remit.</p>
<b>Multiple endocrine neoplasias (MEN)</b>	<p>MEN type I (Wermer's syndrome)—pancreas (e.g., Zollinger-Ellison syndrome, insulinomas, VIPomas), parathyroid, and pituitary tumors (prolactinoma). Presents with kidney stones and stomach ulcers.</p> <p>MEN type II (Sipple's syndrome)—medullary carcinoma of the thyroid, pheochromocytoma, parathyroid tumor.</p> <p>MEN type III (formerly MEN IIb)—medullary carcinoma of the thyroid, pheochromocytoma, and oral and intestinal ganglioneuromatosis (mucosal neuromas).</p>	<p>MEN I = 3 “P” organs (Pancreas, Pituitary, and Parathyroid).</p> <p>All MEN syndromes have autosomal-dominant inheritance.</p> <p>Associated with <i>ret</i> gene in MEN types II and III.</p>
<b>Hypothyroidism and hyperthyroidism</b>		
Hypothyroidism	Cold intolerance, hypoactivity, weight gain, fatigue, lethargy, ↓ appetite, constipation, weakness, ↓ reflexes, myxedema (facial/periorbital), dry, cool skin, and coarse, brittle hair.	↑ TSH (sensitive test for 1° hypothyroidism), ↓ total T <sub>4</sub> , ↓ free T <sub>4</sub> , ↓ T <sub>3</sub> uptake.
Hyperthyroidism	Heat intolerance, hyperactivity, weight loss, chest pain/palpitations, arrhythmias, diarrhea, ↑ reflexes, warm, moist skin, and fine hair.	Riedel's thyroiditis—thyroid replaced by fibrous tissue (hypothyroid). ↓ TSH (if 1°), ↑ total T <sub>4</sub> , ↑ free T <sub>4</sub> , ↑ T <sub>3</sub> uptake.
Graves' disease	An autoimmune hyperthyroidism with thyroid-stimulating/TSH receptor antibodies. Ophthalmopathy (proptosis, EOM swelling), pretibial myxedema, diffuse goiter. Often presents during stress (e.g., childbirth) (see Color Image 71).	Graves' is a type II hypersensitivity.
Thyroid storm	Underlying Graves' disease with a stress-induced catecholamine surge leading to death by arrhythmia.	
<b>Hashimoto's thyroiditis</b>	Autoimmune disorder resulting in hypothyroidism (can have thyrotoxicosis during follicular rupture). Slow course; moderately enlarged, nontender thyroid. Lymphocytic infiltrate with germinal centers. Antimicrosomal and antithyroglobulin antibodies. Hurthle cells.	

<b>Subacute thyroiditis (de Quervain's)</b>	Self-limited hypothyroidism often following a flulike illness. Elevated ESR, jaw pain, early inflammation, and very tender thyroid gland.	May be hyperthyroid early in course.
<b>Toxic multinodular goiter</b>	Iodine deprivation followed by iodine restoration. Causes release of $T_3$ and $T_4$ . Nodules are not malignant. Jod-Basedow phenomenon—thyrotoxicosis if a patient with endemic goiter moves to iodine-replete area.	
<b>Thyroid cancer</b>	1. Papillary carcinoma—most common, excellent prognosis, “ground-glass” nuclei (Orphan Annie), psammoma bodies. Increased risk with childhood irradiation. 2. Follicular carcinoma—good prognosis, uniform follicles. 3. Medullary carcinoma—from parafollicular “C cells”; produces calcitonin, sheets of cells in amyloid stroma. MEN types II and III. 4. Undifferentiated/anaplastic—older patients, very poor prognosis. 5. Lymphoma—associated with Hashimoto's thyroiditis.	
<b>Cretinism</b>	Endemic cretinism occurs wherever endemic goiter is prevalent (lack of dietary iodine); sporadic cretinism is caused by defect in $T_4$ formation or developmental failure in thyroid formation. Findings: pot-bellied, pale, puffy-faced child with protruding umbilicus and protuberant tongue.	Cretin means Christlike (French <i>chrétien</i> ). Those affected were considered so mentally retarded as to be incapable of sinning. Still common in China.
<b>Acromegaly</b>	Excess GH in adults. Findings: large tongue with deep furrows, deep voice, large hands and feet, coarse facial features, impaired glucose tolerance (insulin resistance). $\uparrow$ GH in children $\rightarrow$ gigantism. Treat medically with octreotide.	$\uparrow$ GH is normal in stress, exercise, and hypoglycemia. Test with oral glucose tolerance test.
<b>Hyperparathyroidism</b>		
Primary	Usually an adenoma. Hypercalcemia, hypercalciuria ( <b>renal stones</b> ), hypophosphatemia, $\uparrow$ PTH, $\uparrow$ cAMP in urine. Often asymptomatic, or may present with weakness and constipation (“ <b>groans</b> ”).	“ <b>Stones, bones, and groans.</b> ” <b>Osteitis fibrosa cystica</b> (von Recklinghausen's syndrome)—cystic bone spaces filled with brown fibrous tissue ( <b>bone pain</b> ).
Secondary	$2^\circ$ hyperplasia due to $\downarrow$ serum $Ca^{2+}$ , most often in chronic renal disease. Hypocalcemia, hyperphosphatemia, $\uparrow$ PTH.	<b>Renal osteodystrophy</b> —bone lesions due to $2^\circ$ hyperparathyroidism due in turn to renal disease.
<b>Hypoparathyroidism</b>	Hypocalcemia, tetany. Due to accidental surgical excision (thyroid surgery) or DiGeorge syndrome. Chvostek's sign—tap facial nerve $\rightarrow$ contraction of facial muscles. Trousseau's sign—occlusion of brachial artery with BP cuff $\rightarrow$ carpal spasm.	<b>Pseudohypoparathyroidism</b> —autosomal-dominant kidney unresponsiveness to PTH. Hypocalcemia, shortened 4th/5th digits, short stature.

**Hypercalcemia**

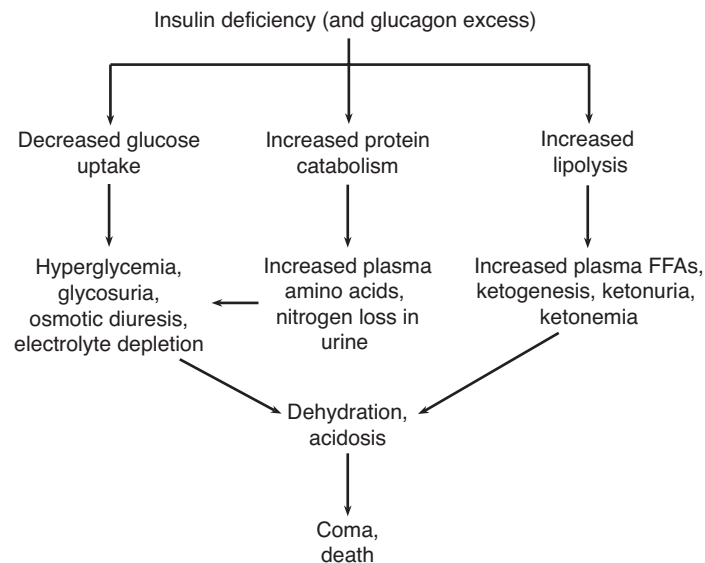
Caused by Calcium ingestion (milk-alkali syndrome), **CHIMPANZEES**.  
Hyperparathyroid, Hyperthyroid, Iatrogenic (thiazides), Multiple myeloma, Paget's disease, Addison's disease, Neoplasms, Zollinger-Ellison syndrome, Excess vitamin D, Excess vitamin A, Sarcoidosis.

**Pituitary adenoma**

Most commonly prolactinoma—amenorrhea, galactorrhea, low libido, infertility. Bromocriptine (dopamine agonist) causes shrinkage.

**Diabetes mellitus**

Acute manifestations Polydipsia, polyuria, polyphagia, weight loss, DKA (type 1), hyperosmolar coma (type 2), unopposed secretion of GH and epinephrine (exacerbating hyperglycemia).



Chronic manifestations

Nonenzymatic glycosylation:  
1. Small vessel disease (diffuse thickening of basement membrane) → retinopathy (hemorrhage, exudates, microaneurysms, vessel proliferation), glaucoma, nephropathy (nodular sclerosis, progressive proteinuria, chronic renal failure, arteriosclerosis leading to hypertension, Kimmelstiel-Wilson nodules)  
2. Large vessel atherosclerosis, CAD, peripheral vascular occlusive disease and gangrene, cerebrovascular disease

Osmotic damage:

1. Neuropathy (motor, sensory, and autonomic degeneration)
2. Cataracts (sorbitol accumulation)

Tests

Fasting serum glucose, glucose tolerance test, HbA<sub>1c</sub> (measures long-term diabetic control).

**Type 1 vs. type 2 diabetes mellitus**

Variable	Type 1—juvenile onset (IDDM)	Type 2—adult onset (NIDDM)
1° defect	Viral or immune destruction of $\beta$ cells (see Color Image 67)	$\uparrow$ resistance to insulin
Insulin necessary in treatment	Always	Sometimes
Age (exceptions commonly occur)	< 30	> 40
Association with obesity	No	Yes
Genetic predisposition	Weak, polygenic	Strong, polygenic
Association with HLA system	Yes (HLA-DR3 and 4)	No
Glucose intolerance	Severe	Mild to moderate
Ketoacidosis	Common	Rare
$\beta$ -cell numbers in the islets	$\downarrow$	Variable
Serum insulin level	$\downarrow$	Variable
Classic symptoms of polyuria, polydipsia, thirst, weight loss	Common	Sometimes

<b>Diabetic ketoacidosis</b>	One of the most important complications of type 1 diabetes. Usually due to an $\uparrow$ in insulin requirements from an $\uparrow$ in stress (e.g., infection). Excess fat breakdown and $\uparrow$ ketogenesis from the $\uparrow$ in free fatty acids, which are then made into ketone bodies.
Signs/symptoms	Kussmaul respirations (rapid/deep breathing), hyperthermia, nausea/vomiting, abdominal pain, psychosis/dementia, dehydration. Fruity breath odor (due to exhaled acetone).
Labs	Hyperglycemia, $\uparrow$ $H^+$ , $\downarrow$ $HCO_3^-$ (anion gap metabolic acidosis), $\uparrow$ blood ketone levels, leukocytosis. Hyperkalemia, but depleted intracellular $K^+$ .
Complications	Life-threatening mucormycosis, <i>Rhizopus</i> infection, cerebral edema, cardiac arrhythmias, heart failure.
Treatment	Fluids, insulin, and potassium; glucose if necessary to prevent hypoglycemia.

<b>Diabetes insipidus</b>	Characterized by intensive thirst and polyuria together with an inability to concentrate urine owing to lack of ADH (central DI—pituitary tumor, trauma, surgery, histiocytosis X) or to a lack of renal response to ADH (nephrogenic DI—hereditary or 2° to hypercalcemia, lithium, demeclocycline).
Diagnosis	Water deprivation test—urine osmolality doesn't $\uparrow$ .
Findings	Urine specific gravity < 1.006; serum osmolality > 290 mOsm/L.
Treatment	Adequate fluid intake. For central DI—intranasal desmopressin (ADH analog). For nephrogenic DI—hydrochlorothiazide, indomethacin, or amiloride.

<b>SIADH</b>	<p>Syndrome of inappropriate antidiuretic hormone secretion:</p> <ol style="list-style-type: none"> <li>1. Excessive water retention</li> <li>2. Hyponatremia</li> <li>3. Urine osmolarity &gt; serum osmolarity</li> </ol> <p>Very low serum sodium levels can lead to seizures (correct slowly). Treat with demeclocycline or H<sub>2</sub>O restriction.</p>	<p>Causes include:</p> <ol style="list-style-type: none"> <li>1. Ectopic ADH (small cell lung cancer)</li> <li>2. CNS disorders/head trauma</li> <li>3. Pulmonary disease</li> <li>4. Drugs (e.g., cyclophosphamide)</li> </ol>
<b>Carcinoid syndrome</b>	<p>Rare syndrome caused by carcinoid tumors (neuroendocrine cells), especially metastatic small bowel tumors, which secrete high levels of serotonin (5-HT). Not seen if tumor is limited to GI tract (5-HT undergoes first-pass metabolism in liver). Results in recurrent <b>diarrhea, cutaneous flushing, asthmatic wheezing, and right-sided valvular disease</b>. Most common tumor of appendix. ↑ 5-HIAA in urine.</p>	<p><b>Rule of 1/3s:</b></p> <p>1/3 metastasize 1/3 present with 2nd malignancy 1/3 multiple</p> <p>Derived from neuroendocrine cells of GI tract. Treat with octreotide.</p>
<b>Zollinger-Ellison syndrome</b>	<p>Gastrin-secreting tumor of pancreas or duodenum. Causes recurrent ulcers. May be associated with MEN type I.</p>	

## Diabetes drugs

Treatment strategy for type 1 DM—low-sugar diet, insulin replacement.

Treatment strategy for type 2 DM—dietary modification and exercise for weight loss; oral hypoglycemics.

Drug Classes	Action	Clinical Use	Toxicities
<b>Insulin:</b> Lispro (short-acting) Insulin (short-acting) NPH (intermediate) Lente (long-acting) Ultralente (long-acting)	<b>Binds insulin receptor</b> (tyrosine kinase activity). Liver: ↑ glucose stored as glycogen. Muscle: ↑ glycogen and protein synthesis, K <sup>+</sup> uptake. Fat: aids TG storage.	Type 1 DM. Also life-threatening hyperkalemia and stress-induced hyperglycemia.	Hypoglycemia, hypersensitivity reaction (very rare).
<b>Sulfonylureas:</b> First generation: Tolbutamide Chlorpropamide Second generation: Glyburide Glimepiride Glipizide	Close K <sup>+</sup> channel in β-cell membrane, so cell depolarizes → <b>triggering of insulin release</b> via ↑ Ca <sup>2+</sup> influx.	Stimulate release of endogenous insulin in type 2 DM. Require some islet function, so useless in type 1 DM.	First generation: disulfiram-like effects. Second generation: hypoglycemia.
<b>Biguanides:</b> Metformin	Exact mechanism is unknown. Possibly ↓ <b>gluconeogenesis</b> , ↑ glycolysis, ↓ serum glucose levels.	Used as oral hypoglycemic. Can be used in patients without islet function.	Most grave adverse effect is lactic acidosis.
<b>Glitazones:</b> Pioglitazone Rosiglitazone	↑ target cell response to insulin.	Used as monotherapy in type 2 DM or combined with above agents.	Weight gain, edema. Hepatotoxicity (troglitazone—no longer used).
<b>α-glucosidase inhibitors:</b> Acarbose Miglitol	<b>Inhibit intestinal brush border α-glucosidases.</b> Delayed sugar hydrolysis and glucose absorption lead to ↓ postprandial hyperglycemia.	Used as monotherapy in type 2 DM in combination with above agents.	GI disturbances.

## Orlistat

Mechanism	Alters fat metabolism by inhibiting pancreatic lipases.
Clinical use	Long-term obesity management (in conjunction with modified diet).
Toxicity	Steatorrhea, GI discomfort, reduced absorption of fat-soluble vitamins, headache.

## Sibutramine

Mechanism	Sympathomimetic serotonin and norepinephrine reuptake inhibitor.
Clinical use	Short-term and long-term obesity management.
Toxicity	Hypertension and tachycardia.



**Propylthiouracil, methimazole**

Mechanism	Inhibit organification and coupling of thyroid hormone synthesis. Propylthiouracil also ↓ peripheral conversion of T <sub>4</sub> to T <sub>3</sub> .
Clinical use	Hyperthyroidism.
Toxicity	Skin rash, agranulocytosis (rare), aplastic anemia.

**Other hypothalamic/pituitary drugs**

Drug	Clinical use
GH	GH deficiency, Turner's syndrome
Somatostatin (octreotide)	Acromegaly, carcinoid, gastrinoma, glucagonoma
Oxytocin	Stimulates labor, uterine contractions, milk let-down; controls uterine hemorrhage
ADH (desmopressin)	Pituitary (central, not nephrogenic) DI

**Levothyroxine, triiodothyronine**

Mechanism	Thyroxine replacement.
Clinical use	Hypothyroidism, myxedema.
Toxicity	Tachycardia, heat intolerance, tremors.

**Glucocorticoids**

Mechanism	Hydrocortisone, prednisone, triamcinolone, dexamethasone, beclomethasone. ↓ the production of leukotrienes and prostaglandins by inhibiting phospholipase A <sub>2</sub> and expression of COX-2.
Clinical use	Addison's disease, inflammation, immune suppression, asthma.
Toxicity	Iatrogenic Cushing's syndrome—buffalo hump, moon facies, truncal obesity, muscle wasting, thin skin, easy bruisability, osteoporosis, adrenocortical atrophy, peptic ulcers, diabetes (if chronic).

# Gastrointestinal

*"A good set of bowels is worth more to a man than any quantity of brains."*  
—Josh Billings

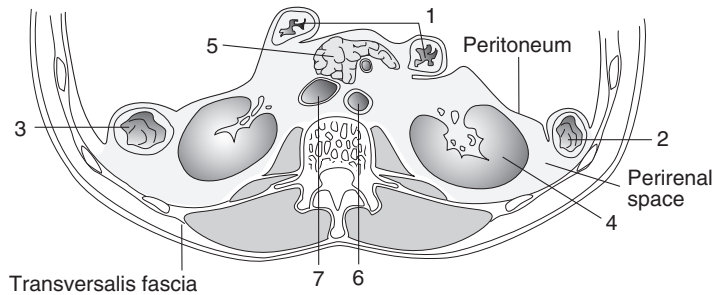
*"Man should strive to have his intestines relaxed all the days of his life."*  
—Moses Maimonides

*"The colon is the playing field for all human emotions."*  
—Cyrus Kapadia, MD

- ▶ High-Yield Clinical Vignettes
- ▶ Anatomy
- ▶ Physiology
- ▶ Pathology
- ▶ Pharmacology

- |                                                                                                                                                      |                                             |                                                                      |
|------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------|----------------------------------------------------------------------|
| ■ Baby vomits milk when fed and has a gastric air bubble.                                                                                            | What kind of fistula is present?            | Blind esophagus with lower segment of esophagus attached to trachea. |
| ■ After a stressful life event, 30-year-old man has diarrhea and blood per rectum; intestinal biopsy shows transmural inflammation.                  | What is the diagnosis?                      | Crohn's disease.                                                     |
| ■ Young man presents with mental deterioration and tremors. He has brown pigmentation in a ring around the periphery of his cornea and altered LFTs. | What treatment should he receive?           | Penicillamine for Wilson's disease.                                  |
| ■ 20-year-old male presents with idiopathic hyperbilirubinemia.                                                                                      | What is the most common cause?              | Gilbert's disease.                                                   |
| ■ 55-year-old male with chronic GERD presents with esophageal cancer.                                                                                | What is the most likely histologic subtype? | Adenocarcinoma.                                                      |
| ■ Female presents with alternating bouts of painful diarrhea and constipation. Colonoscopy is normal.                                                | What is the most likely diagnosis?          | Irritable bowel syndrome.                                            |

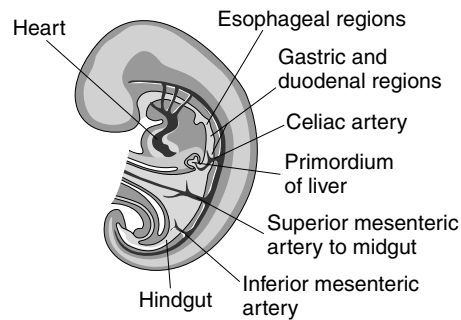
### Retroperitoneal structures



1. Duodenum (2nd, 3rd, 4th parts)
  2. Descending colon
  3. Ascending colon
  4. Kidney and ureters
  5. Pancreas (except tail)
  6. Aorta
  7. IVC
- Adrenal glands and rectum (not shown in diagram)

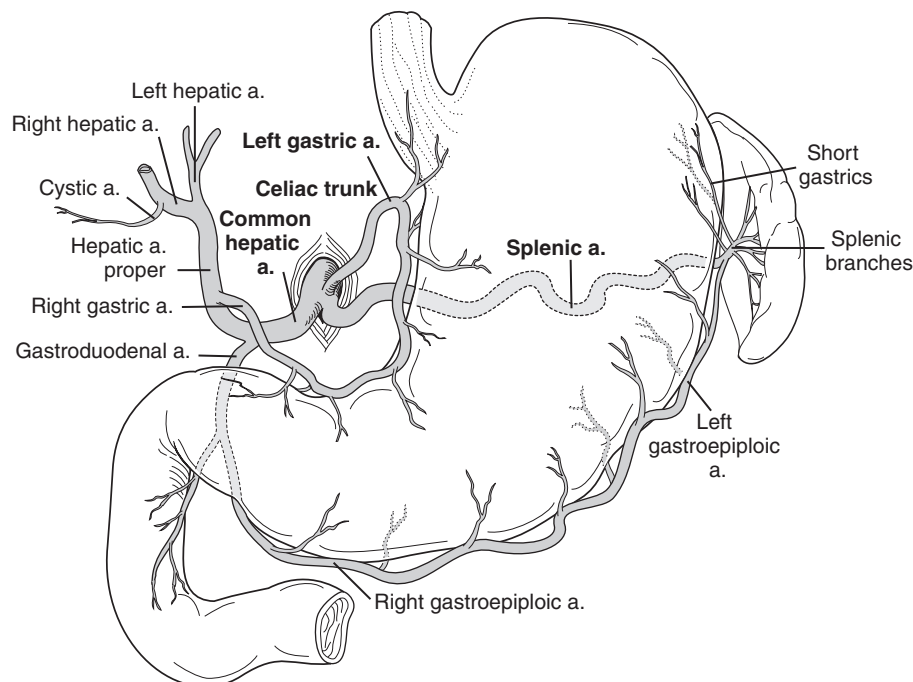
### GI blood supply

Artery	Embryonic gut region	Structures supplied
Celiac	Foregut	Stomach to proximal duodenum; liver, gallbladder, pancreas
SMA	Midgut	Distal duodenum to proximal $\frac{2}{3}$ of transverse colon
IMA	Hindgut	Distal $\frac{1}{3}$ of transverse colon to upper portion of rectum



### Celiac trunk

Branches of celiac trunk: common hepatic, splenic, left gastric. These comprise the main blood supply of the stomach.



Strong anastomoses exist between:

- L and R gastroepiploics
- L and R gastrics

Short gastrics have poor anastomoses if splenic artery is blocked.

**Collateral circulation** If the abdominal aorta is blocked, these arterial anastomoses (with origin) compensate:

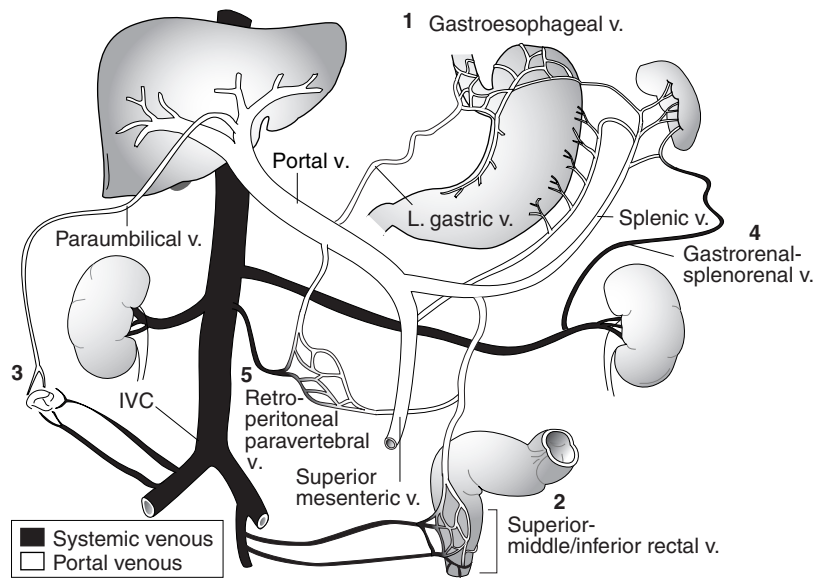
Internal thoracic/mammary (subclavian) ↔ Superior epigastric (internal thoracic) ↔ Inferior epigastric (external iliac)

Superior pancreaticoduodenal (celiac trunk) ↔ Inferior pancreaticoduodenal (SMA)

Middle colic (SMA) ↔ Left colic (IMA)

Superior rectal (IMA) ↔ Middle rectal (internal iliac)

**Portal-systemic anastomoses**



1. Left gastric → azygous (esophageal varices)

2. Superior → inferior rectal (external hemorrhoids)

3. Paraumbilical → inferior epigastric (**caput medusae** at navel)

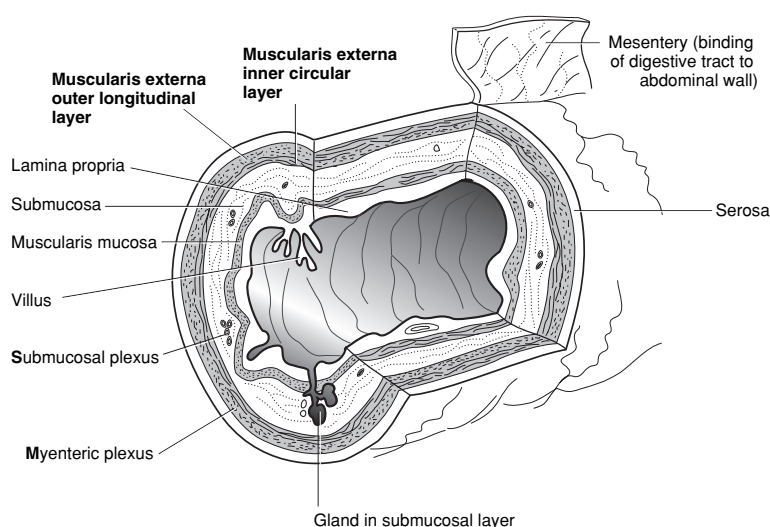
4. Retroperitoneal → renal

5. Retroperitoneal → paravertebral

Varices of **gut**, **butt**, and **caput** are commonly seen with portal hypertension.

**Important GI ligaments**

Ligament	Connects	Structures contained	Notes
Falciform	Liver to anterior abdominal wall	Ligamentum teres	See Embryology chapter
Hepatoduodenal	Liver to duodenum	Portal triad: hepatic artery, portal vein, common bile duct	May be compressed between thumb and index finger placed in epiploic foramen (of Winslow) to control bleeding
Gastrohepatic	Liver to lesser curvature of stomach	Gastric arteries	Separates R greater and lesser sacs May be cut during surgery to access lesser sac
Gastrocolic	Greater curvature and transverse colon	Gastroepiploic arteries	Part of greater omentum
Gastrosplenic	Greater curvature and spleen	No vessels	Separates L greater and lesser sacs
Splenorenal	Spleen to posterior abdominal wall	Splenic artery and vein	

**Digestive tract anatomy**

Layers of gut wall (inside to outside):

1. **Mucosa**—epithelium (absorption), lamina propria (support), muscularis mucosa (motility)
2. **Submucosa**—includes Submucosal nerve plexus
3. **Muscularis externa**—includes Myenteric nerve plexus (Auerbach's)
4. **Serosa/adventitia**

Frequencies of basal electric rhythm:

Stomach—3 Hz  
Duodenum—12 Hz  
Ileum—8–9 Hz

(Adapted, with permission, from McPhee S et al. *Pathophysiology of Disease: An Introduction to Clinical Medicine*, 3rd ed. New York: McGraw-Hill, 2000:296.)

### Enteric nerve plexi

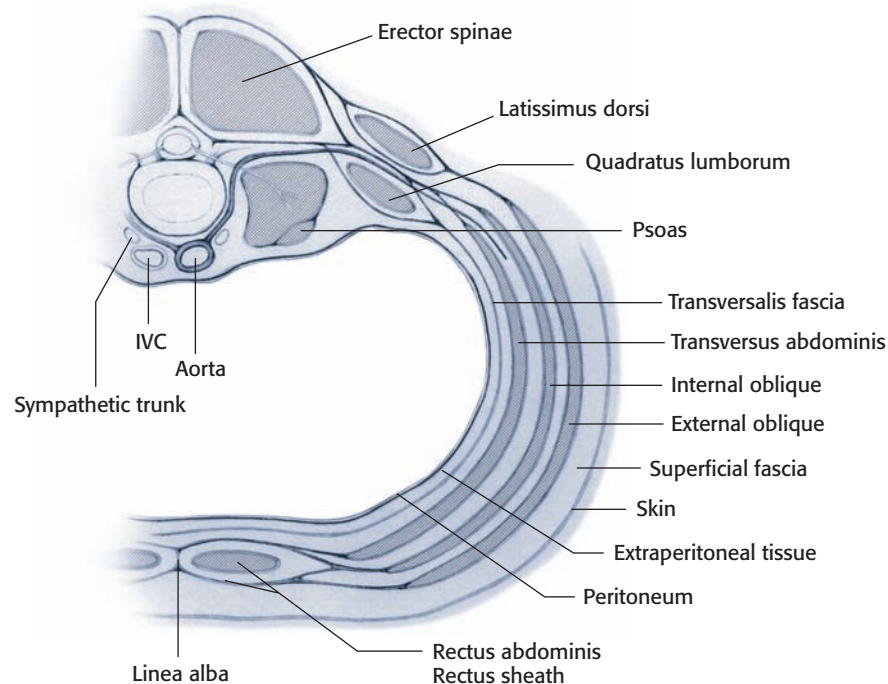
Myenteric  
(Auerbach's)

Coordinates **Motility** along entire gut wall. Contains cell bodies of some parasympathetic terminal effector neurons. Located between inner (circular) and outer (longitudinal) layers of smooth muscle in GI tract wall.

Submucosal  
(Meissner's)

Regulates local **Secretions**, blood flow, and absorption. Contains cell bodies of some parasympathetic terminal effector neurons. Located between mucosa and inner layer of smooth muscle in GI tract wall.

### Abdominal layers



(Reproduced, with permission, from White JS. *USMLE Road Map: Gross Anatomy*, 1st ed. New York: McGraw-Hill, 2003:67.)

### Brunner's glands

Secrete alkaline mucus to neutralize acid contents entering the duodenum from the stomach. Located in **duodenal submucosa** (the only GI submucosal glands). Hypertrophy of Brunner's glands is seen in peptic ulcer disease.

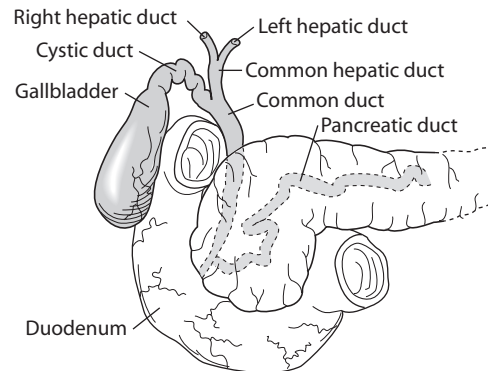
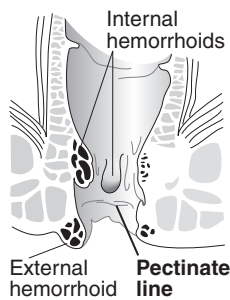
### Peyer's patches

Unencapsulated lymphoid tissue found in lamina propria and submucosa of small intestine. Contain specialized M cells that take up antigen. Stimulated B cells leave Peyer's patch and travel through lymph and blood to lamina propria of intestine, and differentiate into IgA-secreting plasma cells in mesenteric lymph nodes. IgA receives protective secretory component and is then transported across epithelium to gut to deal with intraluminal antigen.

Think of **IgA**, the **I**ntra-gut **A**ntibody. And always say "secretory IgA."

**Sinusoids of liver**

Irregular “capillaries” with fenestrated endothelium (pores 100–200 nm in diameter). No basement membrane. Allow macromolecules of plasma full access to basal surface of hepatocytes through perisinusoidal space (space of Disse).

**Biliary structures****Pectinate line**

Formed where hindgut meets ectoderm.

**Above pectinate line**—internal hemorrhoids, adenocarcinoma. Arterial supply from superior rectal artery (branch of IMA). Venous drainage is to superior rectal vein → inferior mesenteric vein → portal system.

Internal hemorrhoids receive visceral innervation, and are therefore NOT painful.

**Below pectinate line**—external hemorrhoids (painful), squamous cell carcinoma. Somatic innervation. Arterial supply from inferior rectal artery (branch of internal pudendal artery). Venous drainage to inferior rectal vein → internal pudendal vein → internal iliac vein → IVC.

External hemorrhoids receive somatic innervation and are therefore painful.

**Femoral region**

Organization

Lateral to medial: Nerve-(Artery-Vein-Empty space-Lymphatics)

N-(A)VEL

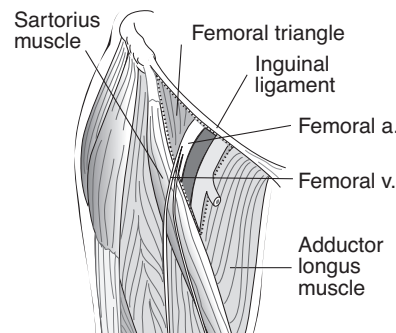
Femoral triangle

Contains femoral vein, artery, nerve

Femoral sheath

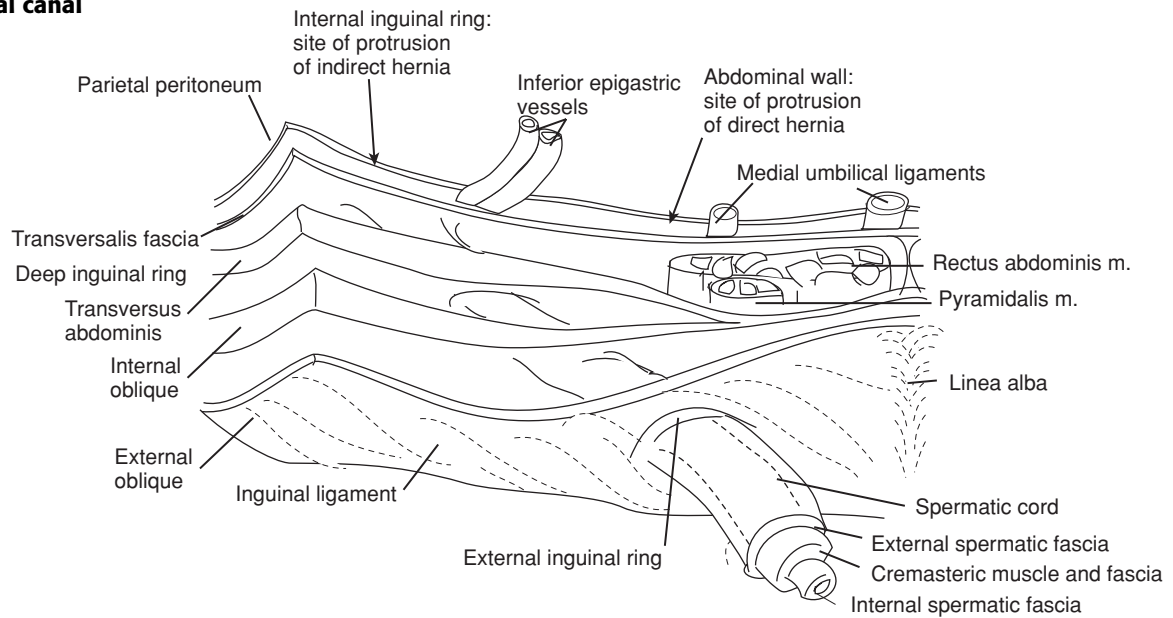
Fascial tube 3–4 cm below inguinal ligament

Contains femoral vein, artery, and canal (deep inguinal lymph nodes), but **not** femoral nerve





## Inguinal canal



(Adapted, with permission, from White JS. *USMLE Road Map: Gross Anatomy*, 1st ed. New York: McGraw-Hill, 2003:69.)

**Hernias**

A hernia is a protrusion of peritoneum through an opening, usually sites of weakness.

**Diaphragmatic hernia**

Abdominal structures enter the thorax; may occur in infants as a result of defective development of pleuroperitoneal membrane. Most commonly a **hiatal hernia**, in which stomach herniates upward through the esophageal hiatus of the diaphragm.

**Hiatal hernias: Sliding** (most common): GE junction is displaced

**Paraesophageal:** GE junction is normal. Cardia moves into the thorax.

**Indirect inguinal hernia**

Goes through the **I**Nternal (deep) inguinal ring, external (superficial) inguinal ring, and **I**Nto the scrotum. Enters internal inguinal ring lateral to inferior epigastric artery. Occur in **I**Nfants owing to failure of processus vaginalis to close. Much more common in males.

Follows the path of the descent of the testes. Covered by all three layers of spermatic fascia.

**Direct inguinal hernia**

Protrudes through the inguinal (Hesselbach's) triangle. Bulges directly through abdominal wall medial to inferior epigastric artery. Goes through the external (superficial) inguinal ring only. Covered by transversalis fascia. Usually in older men.

**MDs don't LIe:**

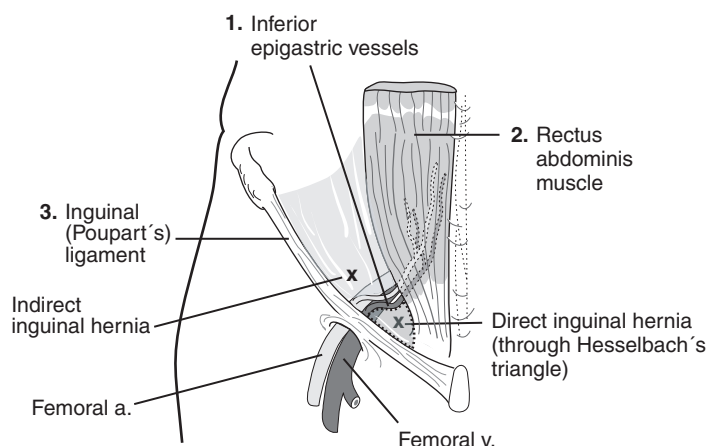
**Medial** to inferior epigastric artery = **D**irect hernia.

**Lateral** to inferior epigastric artery = **I**ndirect hernia.

**Femoral hernia**

Protrudes through femoral canal below and lateral to pubic tubercle. More common in women.

Leading cause of bowel incarceration



**Hesselbach's triangle:**

Inferior epigastric artery

Lateral border of rectus abdominis

Inguinal ligament

### Salivary secretion

Source	Parotid (most serous), submandibular, submaxillary, and sublingual (most mucinous) glands.	Salivary secretion is stimulated by both sympathetic (T1–T3 superior cervical ganglion) and parasympathetic (facial, glossopharyngeal nerve) activity.
Function	<ol style="list-style-type: none"> <li>1. <math>\alpha</math>-amylase (ptyalin) begins starch digestion; inactivated by low pH on reaching stomach</li> <li>2. Bicarbonate neutralizes oral bacterial acids, maintains dental health</li> <li>3. Mucins (glycoproteins) lubricate food</li> </ol>	Low flow rate → hypotonic. High flow rate → closer to isotonic.

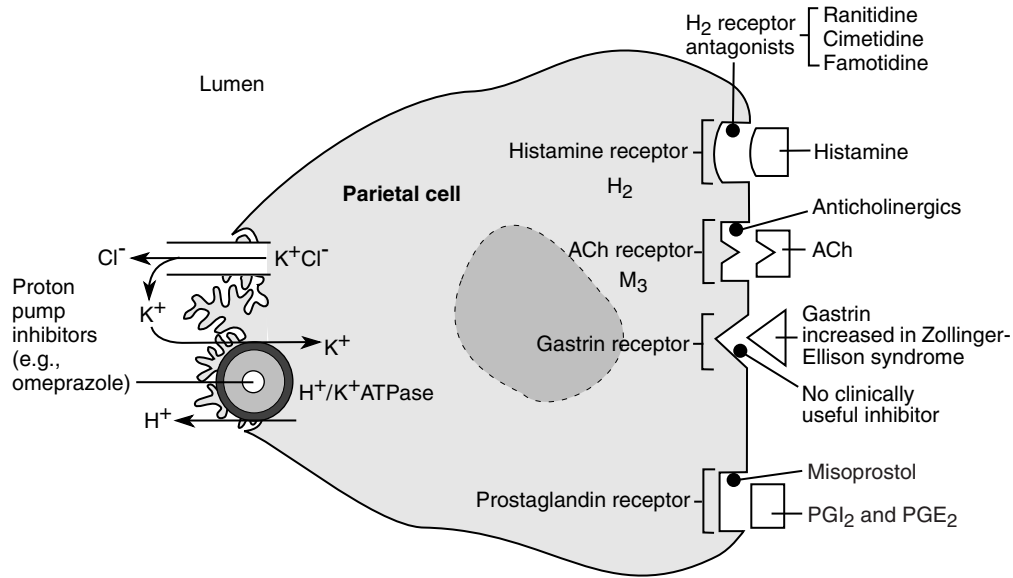
### GI secretory products

Product	Source	Action	Regulation	Notes
Intrinsic factor	Parietal cells Stomach	Vitamin B <sub>12</sub> binding protein (required for B <sub>12</sub> uptake in terminal ileum)		Autoimmune destruction of parietal cells → chronic gastritis and pernicious anemia.
Gastric acid	Parietal cells Stomach	↓ stomach pH	↑ by histamine, ACh, gastrin ↓ by somatostatin, GIP, prostaglandin, secretin	
Pepsin	Chief cells Stomach	Protein digestion	↑ by vagal stimulation, local acid	Inactive pepsinogen → pepsin by H <sup>+</sup> .
HCO <sub>3</sub> <sup>-</sup>	Mucosal cells Stomach Duodenum	Neutralizes acid Prevents autodigestion	↑ by secretin	

**GI hormones**

Hormone	Source	Action	Regulation	Notes
Gastrin	G cells Antrum of stomach	↑ gastric H <sup>+</sup> secretion ↑ growth of gastric mucosa ↑ gastric motility	↑ by stomach distention, amino acids, peptides, vagal stimulation ↓ by stomach pH < 1.5	↑↑ in Zollinger-Ellison syndrome. Phenylalanine and tryptophan are potent stimulators.
Cholecystokinin	I cells Duodenum Jejunum	↑ pancreatic secretion ↑ gallbladder contraction ↓ gastric emptying	↓ by secretin and stomach pH < 1.5 ↑ by fatty acids, amino acids	In cholelithiasis, pain worsens after fatty food ingestion due to ↑ CCK.
Secretin	S cells Duodenum	↑ pancreatic HCO <sub>3</sub> <sup>-</sup> secretion ↓ gastric acid secretion	↑ by acid, fatty acids in lumen of duodenum	↑ HCO <sub>3</sub> <sup>-</sup> neutralizes gastric acid in duodenum, allowing pancreatic enzymes to function.
Somatostatin	D cells Pancreatic islets GI mucosa	↓ gastric acid and pepsinogen secretion ↓ pancreatic and small intestine fluid secretion ↓ gallbladder contraction ↓ insulin and glucagon release	↑ by acid ↓ by vagal stimulation	Inhibitory hormone. Antigrowth hormone effects (digestion and absorption of substances needed for growth). Used to treat VIPoma and carcinoid tumors.
Gastric inhibitory peptide (GIP)	K cells Duodenum Jejunum	Exocrine: ↓ gastric H <sup>+</sup> secretion Endocrine: ↑ insulin release	↑ by fatty acids, amino acids, oral glucose	An oral glucose load is used more rapidly than the equivalent given by IV.
Vasoactive intestinal polypeptide (VIP)	Parasympathetic ganglia in sphincters, gall bladder, small intestine	↑ intestinal water and electrolyte secretion ↑ relaxation of intestinal smooth muscle and sphincters	↑ by distension and vagal stimulation ↓ by adrenergic input	VIPoma: non-α, non-β islet cell pancreatic tumor that secretes VIP. Copious diarrhea.
Nitric oxide		↑ smooth muscle relaxation, including lower esophageal sphincter		Loss of NO secretion is implicated in ↑ lower esophageal tone of achalasia.

## Regulation of gastric acid secretion



### Pancreatic enzymes

$\alpha$ -amylase—starch digestion, secreted in active form.

Lipase, phospholipase A, colipase—fat digestion.

Proteases (trypsin, chymotrypsin, elastase, carboxypeptidases)—protein digestion, secreted as proenzymes.

Trypsinogen is converted to active enzyme trypsin by **enterokinase**, a duodenal brush-border enzyme. Trypsin activates other proenzymes and more trypsinogen (positive feedback loop).

### Carbohydrate digestion

Salivary amylase	Starts digestion, hydrolyzes $\alpha$ -1,4 linkages to yield disaccharides (maltose, maltotriose, and $\alpha$ -limit dextrins).
Pancreatic amylase	Highest concentration in duodenal lumen, hydrolyzes starch to oligosaccharides and disaccharides.
Oligosaccharide hydrolases	At brush border of intestine, the rate-limiting step in carbohydrate digestion, produce monosaccharides from oligo- and disaccharides.

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**Carbohydrate absorption**

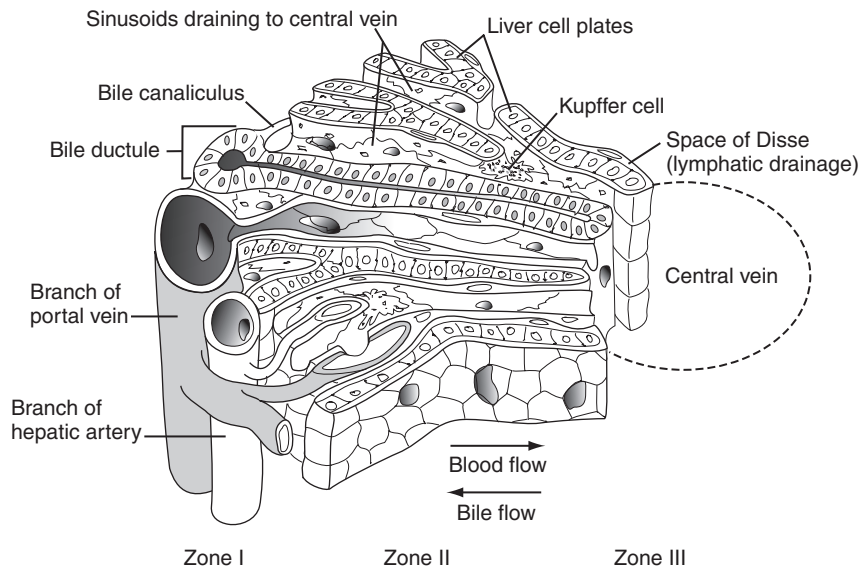
Only monosaccharides (glucose, galactose, fructose) are absorbed by enterocytes. Glucose and galactose are taken up by SGLT1 (Na<sup>+</sup> dependent). Fructose is taken up by facilitated diffusion by GLUT-5. All are transported to blood by GLUT-2.

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**Liver anatomy**

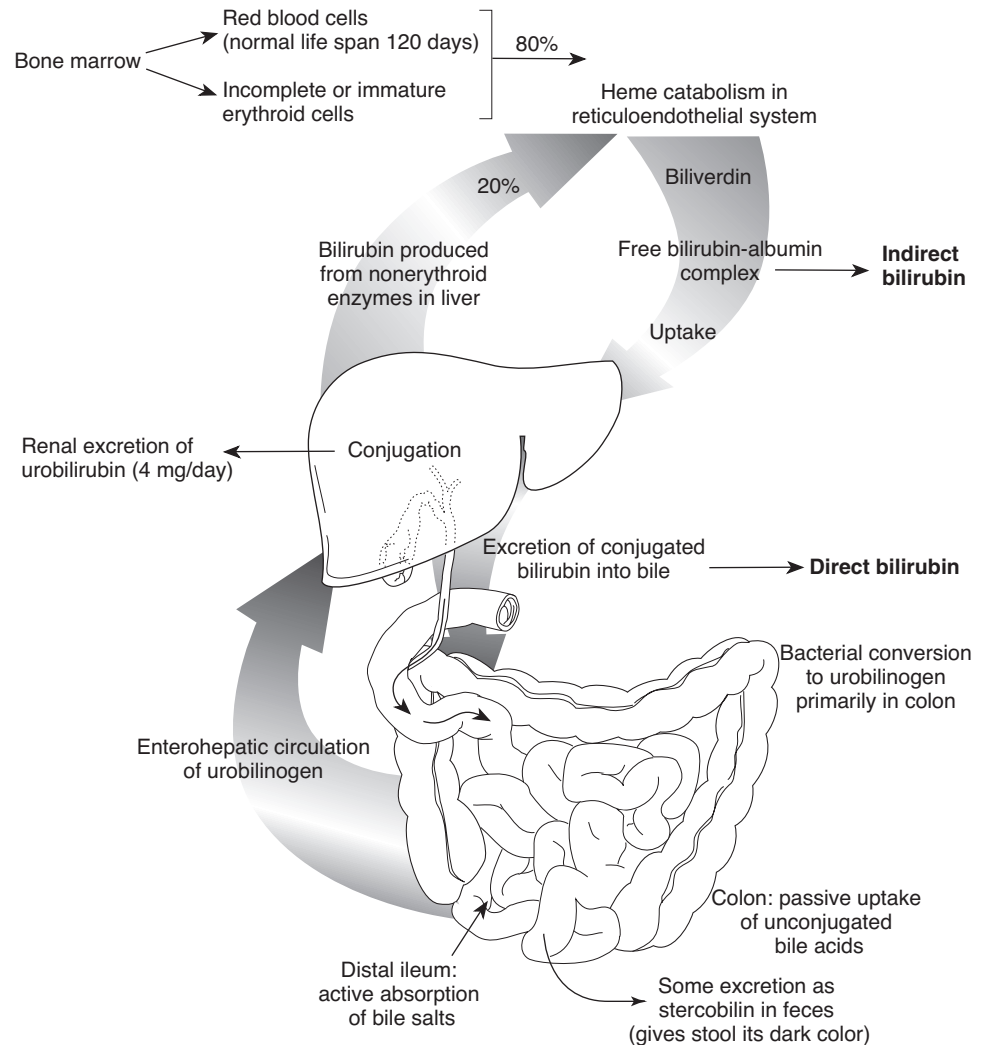
Apical surface of hepatocytes faces bile canaliculi.  
Basolateral surface faces sinusoids.

Zone I: periportal zone  
–most sensitive to toxic injury  
–affected first by viral hepatitis  
Zone II: intermediate zone  
Zone III: pericentral vein zone  
–contains P-450 system  
–affected first by ischemia  
–alcoholic hepatitis



## Bilirubin

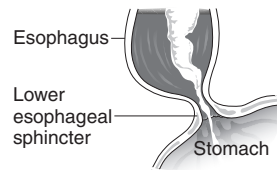
Product of heme metabolism; actively taken up by hepatocytes. Direct bilirubin—conjugated with glucuronic acid; water soluble. Indirect bilirubin—unconjugated; water insoluble. Jaundice (yellow skin, sclerae) results from elevated bilirubin levels.



## Bile

Composed of bile salts (bile acids conjugated to glycine or taurine making them water soluble), phospholipids, cholesterol, bilirubin, water, and ions. The only significant mechanism for cholesterol excretion.

### Achalasia



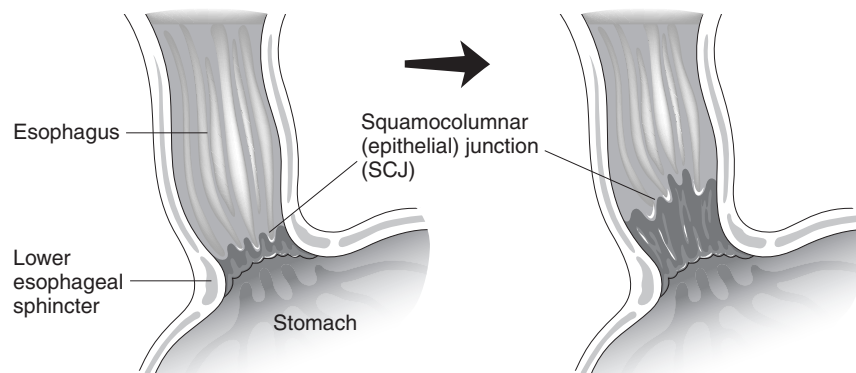
Failure of relaxation of lower esophageal sphincter (LES) due to loss of **myenteric (Auerbach's) plexus**. High LES opening pressure and uncoordinated peristalsis leads to progressive dysphagia. Barium swallow shows dilated esophagus with an area of distal stenosis. Associated with an ↑ risk of esophageal carcinoma.

*A-chalasia* = absence of relaxation.  
2° achalasia may arise from Chagas' disease.  
“Bird beak” on barium swallow.

### Barrett's esophagus

Glandular metaplasia— replacement of nonkeratinized squamous epithelium with intestinal (columnar) epithelium in the distal esophagus. Due to chronic acid reflux.

**BAR**rett's = **B**ecomes **A**denocarcinoma, **R**esults from **R**eflux.



### Esophageal cancer

Risk factors for esophageal cancer are:

- Alcohol
- Barrett's esophagus
- Cigarettes
- Diverticuli (e.g., Zenker's diverticulum)
- Esophageal web (e.g., Plummer-Vinson)/
- Esophagitis (due to reflux, irritants, infection)
- Familial

### ABCDEF.

Worldwide, squamous cell is most common.  
In US, squamous and adenocarcinoma are equal in incidence.

### Congenital pyloric stenosis

Hypertrophy of the pylorus causes obstruction. Palpable “olive” mass in epigastric region and nonbilious projectile vomiting at ≈ 2 weeks of age. Treatment is surgical incision. Occurs in 1/600 live births, often in 1st-born males.



**Malabsorption syndromes**

Celiac sprue	Can cause diarrhea, steatorrhea, weight loss, weakness. Autoantibodies to gluten (gliadin) in wheat and other grains. Proximal small bowel only. Abnormal xylose test. Associated with ↑ risk of T cell lymphoma.
Tropical sprue	Probably infectious; responds to antibiotics. Can affect entire small bowel.
Whipple's disease	Infection with <i>Tropheryma whippelii</i> ; PAS-positive macrophages in intestinal lamina propria, mesenteric nodes. Arthralgias, cardiac, and neurologic symptoms are common. Most often occurs in older men.
Disaccharidase deficiency	Most common is lactase deficiency → milk intolerance. Osmotic diarrhea.
Pancreatic insufficiency	Due to CF, chronic pancreatitis. Causes malabsorption of protein, fat, vitamins A, D, E, K.

**Celiac sprue**

Autoimmune-mediated intolerance of gliadin (wheat) leading to steatorrhea. Associated with people of northern European descent. Findings include blunting of villi, lymphocytes in the lamina propria, and abnormal D-xylose test. Tends to affect jejunum. Associated with dermatitis herpetiformis. 10–15% lead to malignancy (most often T-cell lymphoma).

**Gastritis**

**Acute gastritis (erosive)**

Disruption of mucosal barrier → inflammation. Can be caused by stress, NSAIDs, alcohol, uricemia, burns (Curling's ulcer), and brain injury (Cushing's ulcer).

**Chronic gastritis (nonerosive)**

Type A (fundus/body)

Autoimmune disorder characterized by Autoantibodies to parietal cells, pernicious Anemia, and Achlorhydria.

Type B (antrum)

Caused by *H. pylori* infection. ↑ risk of MALT lymphoma.

**AB pairing**

Pernicious Anemia affects gastric Body.

*H. pylori* Bacterium affects Antrum.

**Peptic ulcer disease**

Gastric ulcer

Pain Greater with meals—weight loss. Often occurs in older patients. *H. pylori* infection in 70%; chronic NSAID use also implicated. Due to ↓ mucosal protection against gastric acid.

Duodenal ulcer

Pain Decreases with meals—weight gain. Almost 100% have *H. pylori* infection. Due to ↑ gastric acid secretion or ↓ mucosal protection. Hypertrophy of Brunner's glands. Tend to have clean, “punched-out” margins unlike the raised/irregular margins of carcinoma. Potential complications include bleeding, penetration, perforation, and obstruction (not intrinsically precancerous) (see Image 111).

**Stomach cancer**

Almost always adenocarcinoma. Early aggressive local spread and node/liver mets. Associated with dietary nitrosamines, achlorhydria, chronic gastritis, type A blood. Termed linitis plastica when diffusely infiltrative (thickened, rigid appearance), signet ring cells.

Virchow's node—involvement of supraclavicular node by mets from stomach. Krukenberg's tumor—bilateral mets to ovaries. Abundant mucus, “signet-ring” cells.

## Inflammatory bowel disease

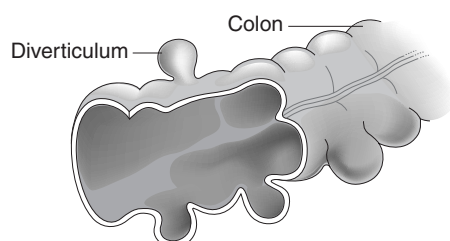
	Crohn's disease	Ulcerative colitis
Possible etiology	Post-infectious.	Autoimmune.
Location	Any portion of the GI tract, usually the terminal ileum and colon. <b>Skip</b> lesions, <b>rectal sparing</b> .	<i>Colitis</i> = colon inflammation. Continuous lesions, always with rectal involvement.
Gross morphology	Transmural inflammation. <b>Cobblestone</b> mucosa, creeping <b>fat</b> , bowel wall thickening ("string sign" on barium swallow x-ray), linear ulcers, fissures, fistulas.	Mucosal and submucosal inflammation only. Friable mucosal pseudopolyps with freely hanging mesentery.
Microscopic morphology	Noncaseating <b>granulomas</b> and lymphoid aggregates.	Crypt abscesses and ulcers, bleeding, no granulomas.
Complications	Strictures, fistulas, perianal disease, malabsorption, nutritional depletion.	Severe stenosis, toxic megacolon, <b>colorectal carcinoma</b> .
Extraintestinal manifestations	Migratory polyarthritis, erythema nodosum, ankylosing spondylitis, uveitis, immunologic disorders.	Pyoderma gangrenosum, 1° sclerosing cholangitis.
For <b>Crohn's</b> , think of a <b>fat granny</b> and an old <b>crone skipping</b> down a <b>cobblestone</b> road away from the <b>wreck</b> (rectal sparing) (see Images 114, 115).		

## Appendicitis

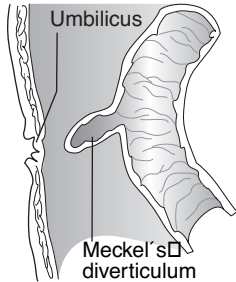
All age groups; most common indication for emergent abdominal surgery in children. Initial diffuse periumbilical pain → localized pain at McBurney's point. Nausea, fever; may perforate → peritonitis.  
Differential: diverticulitis (elderly), ectopic pregnancy (use  $\beta$ -hCG to rule out).

## Diverticular disease

Diverticulum	Blind pouch leading off the alimentary tract, lined by mucosa, muscularis, and serosa, that communicates with the lumen of the gut. Most diverticula (esophagus, stomach, duodenum, colon) are acquired and are termed "false" in that they lack or have an attenuated muscularis externa. Most often in sigmoid colon.	" <b>True</b> " diverticulum—all 3 gut wall layers outpouch. " <b>False</b> " diverticulum or pseudodiverticulum—only mucosa and submucosa outpouch. Occur especially where vasa recta perforate muscularis externa.
Diverticulosis	Many diverticula. Common (in ~50% of people > 60 years). Caused by ↑ intraluminal pressure and focal weakness in colonic wall. Associated with low-fiber diets. Most often in sigmoid colon.	Often asymptomatic or associated with vague discomfort and/or rectal bleeding.
Diverticulitis	Inflammation of diverticula classically causing LLQ pain, fever, leukocytosis. May → perforation, peritonitis, abscess formation, or bowel stenosis (see Color Image 31).	May cause bright red rectal bleeding.



### Meckel's diverticulum



Persistence of the vitelline duct or yolk stalk. May contain ectopic acid-secreting gastric mucosa and/or pancreatic tissue. **Most common congenital anomaly of the GI tract.** Can cause bleeding, intussusception, volvulus, or obstruction near the terminal ileum. Contrast with omphalomesenteric cyst = cystic dilatation of vitelline duct.

The five 2's:  
 2 inches long.  
 2 feet from the ileocecal valve.  
 2% of population.  
 Commonly presents in first 2 years of life.  
 May have 2 types of epithelia (gastric/pancreatic).

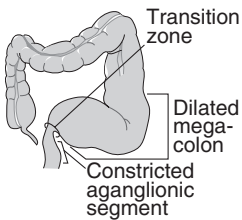
### Zenker's diverticulum

False diverticulum. Herniation of mucosal tissue at junction of pharynx and esophagus. Presenting symptoms: halitosis, dysphagia, obstruction.

### Intussusception and volvulus

Intussusception—"telescoping" of 1 bowel segment into distal segment; can compromise blood supply (see Color Image 34). Often due to intraluminal mass.  
 Volvulus—twisting of portion of bowel around its mesentery; can lead to obstruction and infection. May occur at sigmoid colon, where there is redundant mesentery.

### Hirschsprung's disease



Congenital megacolon characterized by lack of enteric nervous plexus in segment (Auerbach's and Meissner's plexuses) on intestinal biopsy. Due to failure of neural crest cell migration. Presents as chronic constipation early in life. Dilated portion of the colon proximal to the aganglionic segment, resulting in a "transition zone."

Think of a giant spring that has **sprung** in the colon.  
 Risk ↑ with Down syndrome.

### Colonic polyps

90% are benign hyperplastic hamartomas, not neoplasms. Often rectosigmoid. Saw-tooth appearance. The more villous the polyp, the more likely it is to be malignant.

## Colorectal cancer

### Colorectal cancer (CRC)

Third most common cancer. Most are sporadic, due to chromosomal instability (85%) or microsatellite instability (15%).

Risk factors: colorectal villous adenomas, chronic IBD (especially ulcerative colitis, ↑ age), FAP, HNPCC, past medical or family history; screen patients >50 years with stool occult blood test and colonoscopy.

“Apple core” lesion seen on barium swallow x-ray.

CEA tumor marker.

### Familial adenomatous polyposis (FAP)

Autosomal dominant mutation of APC gene on chromosome 5q. Two-hit hypothesis.

Thousands of polyps; pancolonic; always involving the rectum.

**Gardner’s syndrome**—CRC with osseous and soft tissue tumors, retinal hyperplasia.

**Turcot’s syndrome**—CRC with possible brain involvement (glioblastoma).

### HNPCC or Lynch syndrome Peutz-Jeghers

Mutations of DNA repair genes. ~80% progress to CRC. Proximal colon always involved.

Benign polyposis syndrome, not associated with ↑ risk of CRC. However ↑ risk of other visceral malignancies (breast, stomach, ovary).

Findings: hamartomatous polyps of colon and small intestine; hyperpigmented mouth, lips, hands, genitalia.

## Cirrhosis and portal hypertension

### Effects of portal hypertension

- Esophageal varices
  - ↓ Hematemesis
  - ↓ Peptic ulcer
  - ↓ Melena
- Splenomegaly
- Caput medusae
- Ascites
- Hemorrhoids

### Effects of liver cell failure

- Coma
- Scleral icterus
- Feter hepaticus (breath smells like a freshly opened corpse)
- Spider nevi
- Gynecomastia
- Jaundice
- Loss of sexual hair
- Liver “flap” = asterixis (coarse hand tremor)
- Bleeding tendency (decreased prothrombin and clotting factors)
- Anemia
- Ankle edema

(Adapted, with permission, from Chandrasoma P, Taylor CE. *Concise Pathology*, 3rd ed. Stamford, CT: Appleton & Lange, 1998:654.)

*Cirrho* (Greek) = tawny yellow. Diffuse fibrosis of liver, destroys normal architecture.

Nodular regeneration.

**Micronodular**—nodules < 3 mm, uniform size. Due to metabolic insult (e.g., alcohol, hemochromatosis, Wilson’s disease).

**Macronodular**—nodules > 3 mm, varied size. Usually due to significant liver injury leading to hepatic necrosis (e.g., postinfectious or drug-induced hepatitis). ↑ risk of hepatocellular carcinoma.

Portacaval shunt between splenic vein and left renal vein may relieve portal hypertension (see Color Image 29).

► **GASTROINTESTINAL–PATHOLOGY** (*continued*)

<b>Enzyme markers of GI pathology</b>	<b>Serum enzyme</b>	<b>Major diagnostic use</b>
	Aminotransferases (AST and ALT)	Viral hepatitis Alcoholic hepatitis Myocardial infarction (AST)
	GGT ( $\gamma$ -glutamyl transpeptidase)	Various liver diseases
	Alkaline phosphatase	Obstructive liver disease (hepatocellular carcinoma), bone disease
	Amylase	Acute pancreatitis, mumps
	Lipase	Acute pancreatitis
	Ceruloplasmin ( $\downarrow$ )	Wilson's disease (see Color Image 51)
<b>Alcoholic hepatitis</b>	Swollen and necrotic hepatocytes, neutrophil infiltration, Mallory bodies (intracytoplasmic eosinophilic inclusions), fatty change, and sclerosis around central vein (Zone III). SGOT (AST) to SGPT (ALT) ratio is usually $> 1.5$ .	You're toASTed with alcoholic hepatitis. <b>AST</b> $>$ <b>ALT</b> ALT $>$ AST in viral hepatitis.
<b>Budd-Chiari syndrome</b>	Occlusion of IVC or hepatic veins with centrilobular congestion and necrosis, leading to congestive liver disease (hepatomegaly, ascites, abdominal pain, and eventual liver failure). Associated with polycythemia vera, pregnancy, hepatocellular carcinoma.	
<b>Wilson's disease</b>	Inadequate hepatic copper excretion and failure of copper to enter circulation as ceruloplasmin. Leads to copper accumulation, especially in liver, brain, cornea, kidneys, joints. Also known as hepatolenticular degeneration. Wilson's disease is characterized by: Asterixis Basal ganglia degeneration (parkinsonian symptoms) Ceruloplasmin $\downarrow$ , Cirrhosis, Corneal deposits (Kayser-Fleischer rings), Copper accumulation, Carcinoma (hepatocellular), Choreiform movements Dementia	Treat with penicillamine. Autosomal-recessive inheritance.  <b>ABCD.</b>

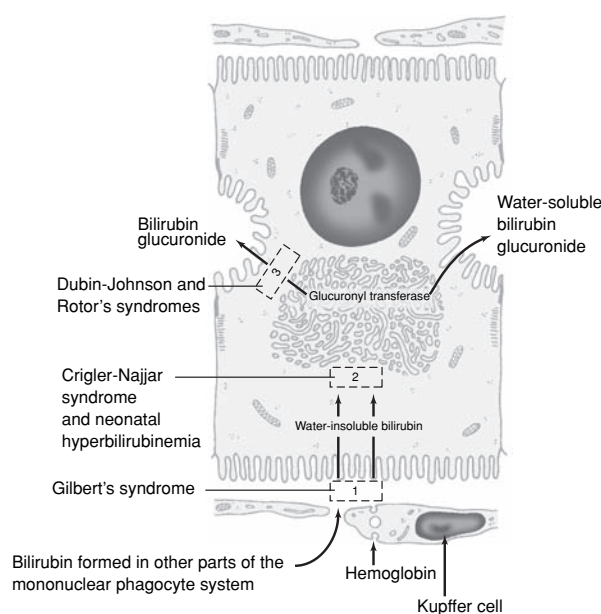
<b>Hemochromatosis</b>	Hemosiderosis is the deposition of hemosiderin (iron); hemochromatosis is the disease caused by this iron deposition. Classic triad of micronodular cirrhosis, pancreatic fibrosis, and skin pigmentation → “ <b>bronze</b> ” diabetes. Results in CHF and ↑ risk of hepatocellular carcinoma. Disease may be 1° (autosomal recessive) or 2° to chronic transfusion therapy. ↑ ferritin, ↑ iron, ↓ TIBC → ↑ transferrin saturation (see Color Image 26).	Total body iron may reach 50 g, enough to set off metal detectors at airports. Treat with repeated phlebotomy, deferoxamine. Associated with HLA A3.
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**Jaundice** Normally, liver cells convert unconjugated (indirect) bilirubin into conjugated (direct) bilirubin. Direct bilirubin is water soluble and can be excreted into urine and by the liver into bile to be converted by gut bacteria to urobilinogen (some of which is reabsorbed). Some urobilinogen is also formed directly from heme metabolism.

Jaundice type	Hyperbilirubinemia	Urine bilirubin	Urine urobilinogen
Hepatocellular	Conjugated/unconjugated	↑	Normal/↓
Obstructive	Conjugated	↑	↓
Hemolytic	Unconjugated	Absent (acholuria)	↑

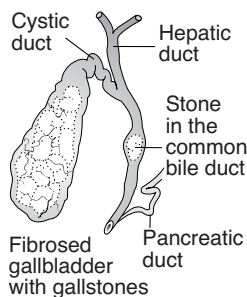
### Hereditary hyperbilirubinemias

Gilbert's syndrome	Mildly ↓ UDP-glucuronyl transferase. Asymptomatic. Elevated unconjugated bilirubin without overt hemolysis. Associated with stress.	No clinical consequences.
Crigler-Najjar syndrome, type I	Absent UDP-glucuronyl transferase. Presents early in life; patients die within a few years. Findings: jaundice, kernicterus (bilirubin deposition in brain), ↑ unconjugated bilirubin. Treatment: plasmapheresis and phototherapy.	Type II is less severe and responds to phenobarbital, which ↑ liver enzyme synthesis.
Dubin-Johnson syndrome	Conjugated hyperbilirubinemia due to defective liver excretion. Grossly black liver. Benign.	Rotor's syndrome is similar but even milder and does not cause black liver.



(Adapted, with permission, from Junqueira LC, Carneiro J, Kelley RO. *Basic Histology*, 9th ed. Stamford, CT: Appleton & Lange, 1999.)

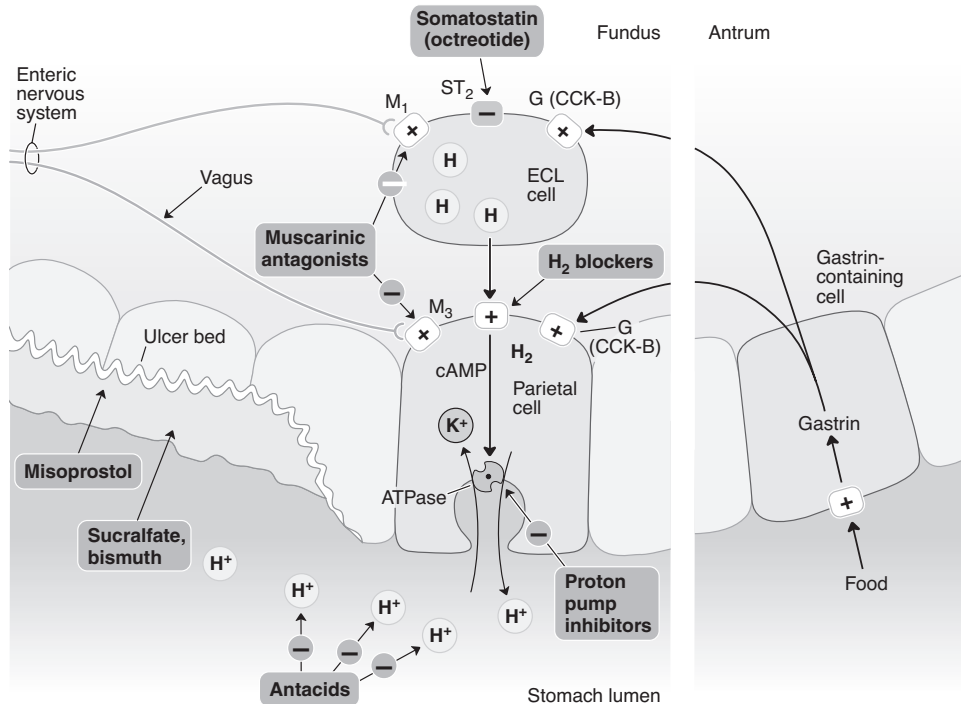
<b>Primary sclerosing cholangitis</b>	Both intra- and extrahepatic. Inflammation and fibrosis of bile ducts → alternating strictures and dilation with “beading” on ERCP. Associated with ulcerative colitis. Can lead to 2° biliary cirrhosis.	Charcot’s triad of cholangitis: 1. Jaundice 2. Fever 3. RUQ pain
<b>Biliary cirrhosis</b>		
Primary	Intrahepatic, autoimmune disorder; severe obstructive jaundice, steatorrhea, pruritus, hypercholesterolemia (xanthoma). ↑ alkaline phosphatase, ↑ serum mitochondrial antibodies. Associated with scleroderma, CREST syndrome.	
Secondary	Due to extrahepatic biliary obstruction. ↑ in pressure in intrahepatic ducts → injury/fibrosis. Often complicated by ascending cholangitis (bacterial infection), bile stasis, and “bile lakes.” ↑ alkaline phosphatase, ↑ conjugated bilirubin.	
<b>Hepatocellular carcinoma/hepatoma</b>	Most common 1° malignant tumor of the liver in adults. ↑ incidence of hepatocellular carcinoma is associated with hepatitis B and C, Wilson’s disease, hemochromatosis, α <sub>1</sub> -antitrypsin deficiency, alcoholic cirrhosis, and carcinogens (e.g., aflatoxin B1). Can present with tender hepatomegaly, ascites, polycythemia, and hypoglycemia.	Commonly spread by hematogenous dissemination. Elevated α-fetoprotein. May lead to Budd-Chiari syndrome.
<b>Reye’s syndrome</b>	Rare, often fatal childhood hepatoencephalopathy. Findings: fatty liver (microvesicular fatty change), hypoglycemia, coma. Associated with viral infection (especially VZV and influenza B) and salicylates. Aspirin is not recommended for children (use acetaminophen, with caution).	
<b>Gallstones</b>	Form when solubilizing bile acids and lecithin are overwhelmed by ↑ cholesterol and/or bilirubin. Three types of stones: 1. <b>Cholesterol stones</b> (radiolucent with 10–20% opaque due to calcifications)—associated with obesity, Crohn’s disease, cystic fibrosis, advanced age, clofibrate, estrogens, multiparity, rapid weight loss, and Native American origin. 2. <b>Mixed stones</b> (radiolucent)—have both cholesterol and pigment components. Most common type. 3. <b>Pigment stones</b> (radiopaque)—seen in patients with chronic RBC hemolysis, alcoholic cirrhosis, advanced age, and biliary infection. Can cause ascending cholangitis, acute pancreatitis, bile stasis, cholecystitis. Diagnose with ultrasound. Treat with cholecystectomy.	Risk factors (4 F’s): 1. Female 2. Fat 3. Fertile 4. Forty



<b>Acute pancreatitis</b>	<p>Autodigestion of pancreas by pancreatic enzymes.</p> <p>Causes: Gallstones, Ethanol, Trauma, Steroids, Mumps, Autoimmune disease, Scorpion sting, Hypercalcemia/Hyperlipidemia, Drugs (e.g., sulfa drugs).</p> <p>Clinical presentation: epigastric abdominal pain radiating to back; anorexia, nausea.</p> <p>Labs: elevated amylase, lipase (higher specificity).</p> <p>Can lead to DIC, ARDS, diffuse fat necrosis, hypocalcemia, pseudocyst formation, hemorrhage, and infection.</p> <p>Chronic calcifying pancreatitis is strongly associated with alcoholism (see Image 135).</p> <p>Chronic obstructive pancreatitis is strongly associated with gallstones.</p>	<b>GET SMASHeD.</b>
<b>Pancreatic adenocarcinoma</b>	<p>Prognosis averages 6 months or less; very aggressive; usually already metastasized at presentation; tumors more common in pancreatic head (obstructive jaundice).          ↑ risk in Jewish and African-American males. Associated with cigarettes, but not ETOH.</p> <p>Often presents with:</p> <ol style="list-style-type: none"> <li>1. Abdominal pain radiating to back</li> <li>2. Weight loss (due to malabsorption and anorexia)</li> <li>3. Migratory thrombophlebitis (Trousseau's syndrome)</li> <li>4. Obstructive jaundice with palpable gallbladder (Courvoisier's sign) (see Image 134)</li> </ol>	
<b>Carcinoid</b>	<p>Tumor of endocrine cells. Comprise 50% of small bowel tumors. Most common site is appendix. "Dense core bodies" seen on EM. Often produce 5-HT. Classic symptoms mentioned on boards: wheezing, right-sided heart lesions, diarrhea, flushing.</p>	



GI therapy



(Adapted, with permission, from Katzung BG, Trevor AJ. *USMLE Road Map: Pharmacology*, 1st ed. New York: McGraw-Hill, 2003:159.)

**H<sub>2</sub> blockers**

Mechanism  
Clinical use  
Toxicity

Cimetidine, ranitidine, famotidine, nizatidine.  
Reversible block of histamine H<sub>2</sub> receptors → ↓ H<sup>+</sup> secretion by parietal cells.  
Peptic ulcer, gastritis, mild esophageal reflux.  
Cimetidine is a potent inhibitor of P-450; it also has antiandrogenic effects (prolactin release, gynecomastia, impotence, ↓ libido in males); can cross BBB (confusion, dizziness, headaches) and placenta. Both cimetidine and ranitidine ↓ renal excretion of creatinine. Other H<sub>2</sub> blockers are relatively free of these effects.

**Proton pump inhibitors**

Mechanism  
Clinical use

Omeprazole, lansoprazole.  
Irreversibly inhibit H<sup>+</sup>/K<sup>+</sup> ATPase in stomach parietal cells.  
Peptic ulcer, gastritis, esophageal reflux, Zollinger-Ellison syndrome.

**Bismuth, sucralfate**

Mechanism  
Clinical use

Bind to ulcer base, providing physical protection, and allow HCO<sub>3</sub><sup>-</sup> secretion to reestablish pH gradient in the mucus layer.  
↑ ulcer healing, traveler's diarrhea.

Triple therapy of *H. pylori* ulcers—metronidazole, bismuth, amoxicillin (or tetracycline).

<b>Misoprostol</b>		
Mechanism	A PGE <sub>1</sub> analog. ↑ production and secretion of gastric mucous barrier, ↓ acid production.	
Clinical use	Prevention of NSAID-induced peptic ulcers; maintenance of a patent ductus arteriosus. Also used to induce labor.	
Toxicity	Diarrhea. Contraindicated in women of childbearing potential (abortifacient).	
<hr/>		
<b>Muscarinic antagonists</b>		
Mechanism	Pirenzepine, propantheline. Block M1 receptors on ECL cells (↓ histamine secretion) and M3 receptors on parietal cells (↓ H <sup>+</sup> secretion).	
Clinical use	Peptic ulcer.	
Toxicity	Tachycardia, dry mouth, difficulty focusing eyes.	
<hr/>		
<b>Antacid overuse</b>		
	Can affect absorption, bioavailability, or urinary excretion of other drugs by altering gastric and urinary pH or by delaying gastric emptying.	
	Overuse can also cause the following problems:	
	1. <b>Aluminum hydroxide</b> —constipation and hypophosphatemia; proximal muscle weakness, osteodystrophy, seizures	<b>Aluminum</b> amount of feces.
	2. <b>Magnesium hydroxide</b> —diarrhea, hyporeflexia, hypotension, cardiac arrest.	<b>Mg = Must go to the bathroom.</b>
	3. <b>Calcium carbonate</b> —hypercalcemia, rebound acid ↑	
	All can cause hypokalemia.	
<hr/>		
<b>Infliximab</b>		
Mechanism	A monoclonal antibody to TNF-α, proinflammatory cytokine.	
Clinical use	Crohn's disease, rheumatoid arthritis.	
Toxicity	Respiratory infection, fever, hypotension.	
<hr/>		
<b>Sulfasalazine</b>		
Mechanism	A combination of sulfapyridine (antibacterial) and mesalamine (anti-inflammatory). Activated by colonic bacteria.	
Clinical use	Ulcerative colitis, Crohn's disease.	
Toxicity	Malaise, nausea, sulfonamide toxicity, reversible oligospermia.	
<hr/>		
<b>Ondansetron</b>		
Mechanism	5-HT <sub>3</sub> antagonist. Powerful central-acting antiemetic.	
Clinical use	Control vomiting postoperatively and in patients undergoing cancer chemotherapy.	You will not vomit with <b>ONDANSetron</b> , so you can go <b>ON DANCing</b> .
Toxicity	Headache, constipation.	

**Pro-kinetic agents**

**Cisapride**

Mechanism	Acts through serotonin receptors to ↑ ACh release at the myenteric plexus. ↑ esophageal tone; ↑ gastric and duodenal contractility, improving transit time (including through the colon).
Toxicity	No longer used. Serious interactions (torsades des pointes) with erythromycin, ketoconazole, nefazodone, fluconazole.

**Metoclopramide**

Mechanism	D <sub>2</sub> receptor antagonist. ↑ resting tone, contractility, LES tone, motility. Does not ↑ transit time through colon.
Clinical use	Diabetic and post-surgery gastroparesis.
Toxicity	↑ parkinsonian effects. Restlessness, drowsiness, fatigue, depression, nausea, constipation. Drug interaction with digoxin and diabetic agents. Contraindicated in patients with small bowel obstruction.

# Hematology and Oncology

*“The best blood will at some time get into a fool or mosquito.”*

—Austin O'Malley

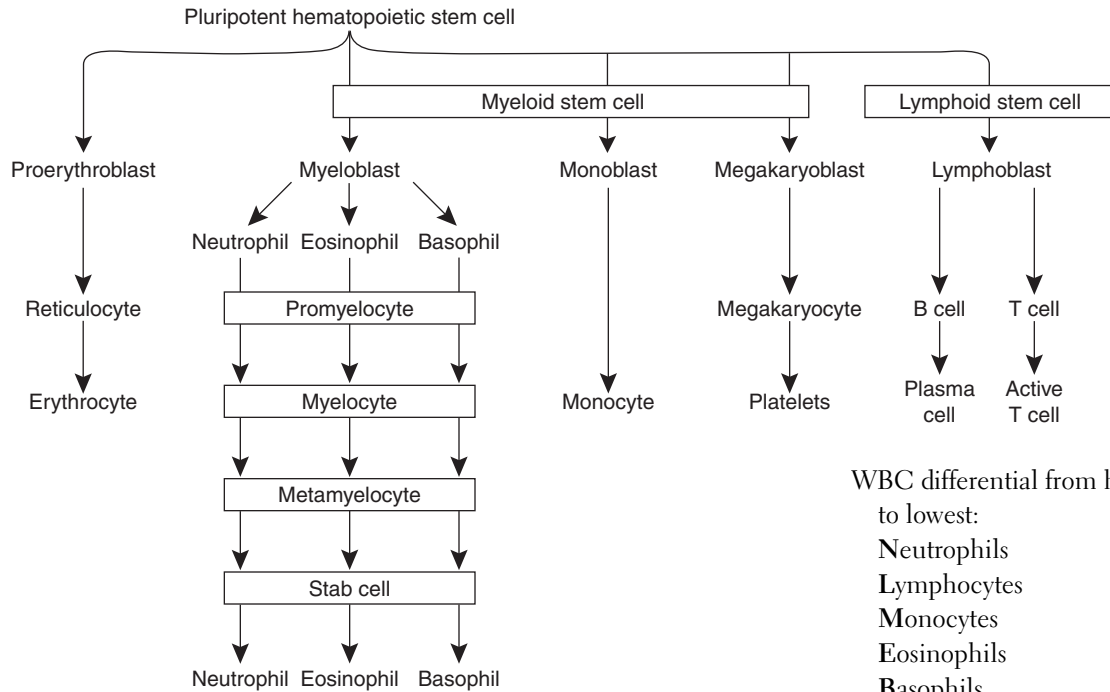
*“A day without blood is like a day without sunshine.”*

—Joker in *Full Metal Jacket*

- ▶ High-Yield Clinical Vignettes
- ▶ Anatomy
- ▶ Physiology
- ▶ Pathology
- ▶ Pharmacology

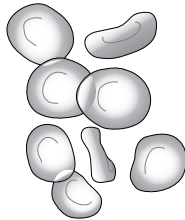
- |                                                                                                                                                                                                                               |                                                                                    |                                                                                              |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>■ Child has been anemic since birth.</li> </ul>                                                                                                                                        | <p>Splenectomy would result in ↑ hematocrit in what disease?</p>                   | <p>Spherocytosis.</p>                                                                        |
| <ul style="list-style-type: none"> <li>■ Patient presents with fatigue, and blood tests show a macrocytic, megaloblastic anemia.</li> </ul>                                                                                   | <p>What is the danger of giving folate alone?</p>                                  | <p>Masks signs of neural damage with vitamin B<sub>12</sub> deficiency.</p>                  |
| <ul style="list-style-type: none"> <li>■ Patient presents with anemia, hypercalcemia, and bone pain on palpation; bone marrow biopsy shows a slide packed with cells that have a large, round, off-center nucleus.</li> </ul> | <p>What is the diagnosis, and what may be found on urinalysis?</p>                 | <p>Multiple myeloma (plasma cell neoplasm); Bence Jones protein (Ig light chains).</p>       |
| <ul style="list-style-type: none"> <li>■ AIDS patient has just been diagnosed with cancer.</li> </ul>                                                                                                                         | <p>What neoplasms are associated with AIDS?</p>                                    | <p>B-cell lymphoma, Kaposi's sarcoma.</p>                                                    |
| <ul style="list-style-type: none"> <li>■ Patient with a new cancer diagnosis and known history of CHF is being evaluated for chemotherapy.</li> </ul>                                                                         | <p>What chemotherapeutic agent should be avoided in this patient?</p>              | <p>Doxorubicin (cardiotoxic).</p>                                                            |
| <ul style="list-style-type: none"> <li>■ Chromosome analysis reveals the presence of the Philadelphia chromosome, t(9;22).</li> </ul>                                                                                         | <p>What is the latest targeted therapy for this disease, and how does it work?</p> | <p>Imatinib (Gleevec) is used to treat CML; inhibitor of <i>bcr-abl</i> tyrosine kinase.</p> |

## Blood cell differentiation



WBC differential from highest to lowest:  
 Neutrophils  
 Lymphocytes  
 Monocytes  
 Eosinophils  
 Basophils  
 Neutrophils Like Making Everything Better.

### Erythrocyte



Anucleate, biconcave → large surface area: volume ratio → easy gas exchange ( $O_2$  and  $CO_2$ ). Source of energy—glucose (90% anaerobically degraded to lactate, 10% by HMP shunt). Survival time—120 days. Membrane contains the chloride-bicarbonate antiport important in the “physiologic chloride shift,” which allows the RBC to transport  $CO_2$  from the periphery to the lungs for elimination.

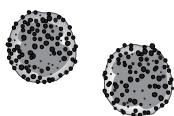
*Eryth* = red; *cyte* = cell.  
 Erythrocytosis = polycythemia = ↑ number of red cells.  
 Anisocytosis = varying sizes.  
 Poikilocytosis = varying shapes.  
 Reticulocyte = immature erythrocyte.

### Leukocyte

Types: granulocytes (basophils, eosinophils, neutrophils) and mononuclear cells (lymphocytes, monocytes). Responsible for defense against infections. Normally 4000–10,000 per microliter.

*Leuk* = white; *cyte* = cell.

### Basophil



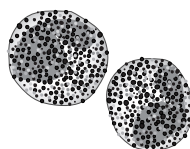
Mediates allergic reaction. < 1% of all leukocytes. Bilobate nucleus. Densely basophilic granules containing heparin (anticoagulant), histamine (vasodilator) and other vasoactive amines, and leukotrienes (LTD-4). Found in the blood.

**Basophilic**—staining readily with **basic** stains.  
 Basophilic stippling is seen in **TAIL**: **T**halassemias, **A**nemia of chronic disease, **I**ron deficiency anemia, and **L**ead poisoning.

► HEMATOLOGY AND ONCOLOGY—ANATOMY (*continued*)**Mast cell**

Mediates allergic reaction. Degranulation—histamine, heparin, and eosinophil chemotactic factors. Can bind IgE to membrane. Mast cells resemble basophils structurally and functionally but are not the same cell type. Found in tissue.

Involved in type I hypersensitivity reactions. Cromolyn sodium prevents mast cell degranulation (used to treat asthma).

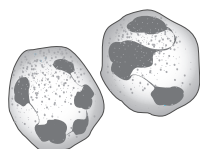
**Eosinophil**

1–6% of all leukocytes. Bilobate nucleus. Packed with large eosinophilic granules of uniform size. Defends against helminthic and protozoan infections (major basic protein). Highly phagocytic for antigen-antibody complexes. Produces histaminase and arylsulfatase.

*Eosin* = a dye; *philic* = loving. Causes of eosinophilia =

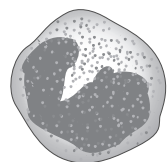
**NAACP:**

- Neoplastic
- Asthma
- Allergic processes
- Collagen vascular diseases
- Parasites

**Neutrophil**

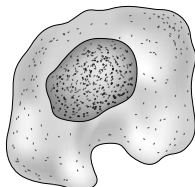
Acute inflammatory response cell. 40–75% WBCs. Phagocytic. Multilobed nucleus. Large, spherical, azurophilic 1° granules (called lysosomes) contain hydrolytic enzymes, lysozyme, myeloperoxidase, and lactoferrin.

Hypersegmented polys are seen in vitamin B<sub>12</sub>/folate deficiency.

**Monocyte**

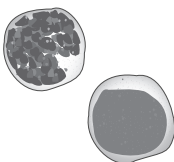
2–10% of leukocytes. Large. Kidney-shaped nucleus. Extensive “frosted glass” cytoplasm. Differentiates into macrophages in tissues.

*Mono* = one (nucleus); *cyte* = cell.

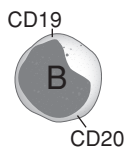
**Macrophage**

Phagocytoses bacteria, cell debris, and senescent red cells and scavenges damaged cells and tissues. Long life in tissues. Macrophages differentiate from circulating blood monocytes. Activated by  $\gamma$ -interferon. Can function as APC via MHC II.

*Macro* = large; *phage* = eater.

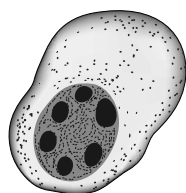
**Lymphocyte**

Round, densely staining nucleus. Small amount of pale cytoplasm. B lymphocytes produce antibodies. T lymphocytes manifest the cellular immune response as well as regulate B lymphocytes and macrophages.

**B lymphocyte**

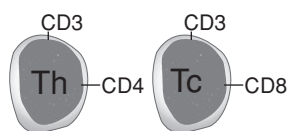
Part of humoral immune response. Arises from stem cells in bone marrow. Matures in marrow. Migrates to peripheral lymphoid tissue (follicles of lymph nodes, white pulp of spleen, unencapsulated lymphoid tissue). When antigen is encountered, B cells differentiate into plasma cells and produce antibodies. Has memory. Can function as antigen-presenting cell (APC) via MHC II.

**B = Bone marrow.**

**Plasma cell**

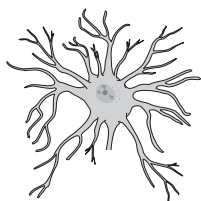
Off-center nucleus, clock-face chromatin distribution, abundant RER and well-developed Golgi apparatus. B cells differentiate into plasma cells, which produce large amounts of antibody specific to a particular antigen.

Multiple myeloma is a plasma cell neoplasm.

**T lymphocyte**

Mediates cellular immune response. Originates from stem cells in the bone marrow, but matures in the thymus. T cells differentiate into cytotoxic T cells (MHC I, CD8), helper T cells (MHC II, CD4), and suppressor T cells.

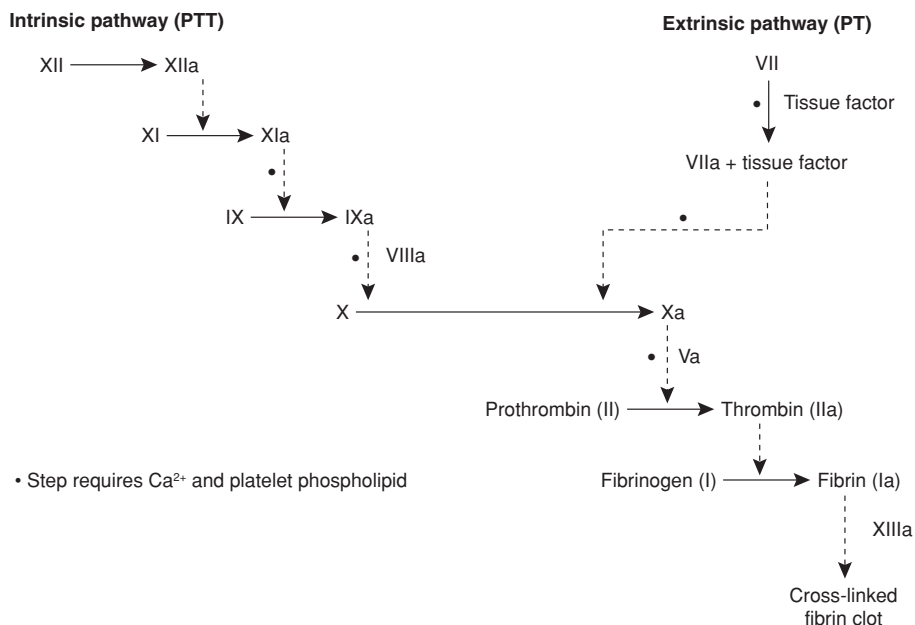
**T** is for Thymus. **CD** is for Cluster of Differentiation. **MHC × CD = 8** (e.g., MHC 2 × CD4 = 8, and MHC 1 × CD8 = 8).

**Dendritic cells**

Professional APCs. Express MHC II and Fc receptor (FcR) on surface. Main inducers of 1° antibody response. Called Langerhans cells on skin.



## Coagulation cascade

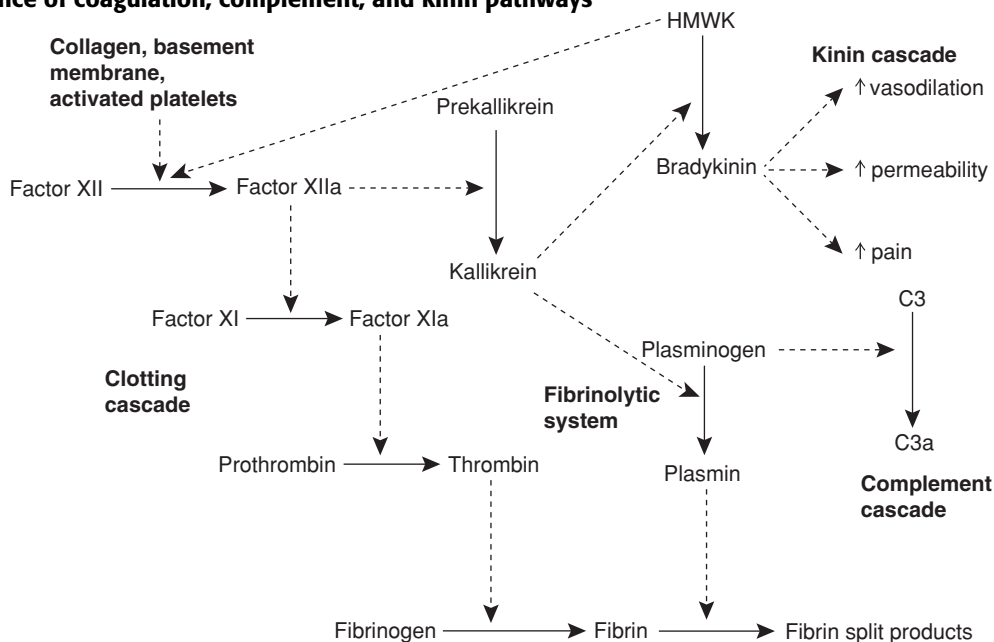


### Coagulation factor inhibitors and fibrinolysis

Protein C and protein S—inactivate Va and VIIIa; vitamin K-dependent.  
 Antithrombin III—inactivates thrombin, IXa, Xa, and XIa; activated by heparin.  
 tPA—generates plasmin, which cleaves fibrin.

Factor V Leiden mutation causes resistance to activated protein C.

## Convergence of coagulation, complement, and kinin pathways



**Blood groups**

A	A antigen on RBC surface and B antibody in plasma.	Rh+ blood transfusions into an Rh- individual can result in massive IgG production.
B	B antigen on RBC surface and A antibody in plasma.	Incompatible blood transfusions can cause immunologic response, hemolysis, renal failure, shock, and death.
AB	A and B antigens on RBC surface, "universal recipient."	
O	Neither A nor B antigen on RBC surface; both antibodies in plasma; "universal donor."	

**RBC forms**

Biconcave	Normal.	
Spherocytes	Hereditary spherocytosis, autoimmune hemolysis.	
Elliptocyte	Hereditary elliptocytosis.	
Macro-ovalocyte	Megaloblastic anemia (also hypersegmented PMNs), marrow failure.	
Helmet cell, schistocyte	DIC, traumatic hemolysis.	
Sickle cell	Sickle cell anemia.	
Teardrop cell	Myeloid metaplasia with myelofibrosis.	
Acanthocyte	Spiny appearance in abetalipoproteinemia.	
Target cell	HbC disease, Asplenia, Liver disease, Thalassemia.	<b>HALT.</b>
Poikilocytes	Nonuniform shapes in TTP/HUS, microvascular damage, DIC.	
Burr cell	TTP/HUS.	

**Psammoma bodies**

Laminated, concentric, calcific spherules seen in:	<b>PSaMMoma:</b>
1. Papillary adenocarcinoma of thyroid	Papillary (thyroid)
2. Serous papillary cystadenocarcinoma of ovary	Serous (ovary)
3. Meningioma	Meningioma
4. Malignant mesothelioma	Mesothelioma

## Anemia

### Type

Microcytic,  
hypochromic  
(MCV < 80)

Macrocytic  
(MCV > 100)

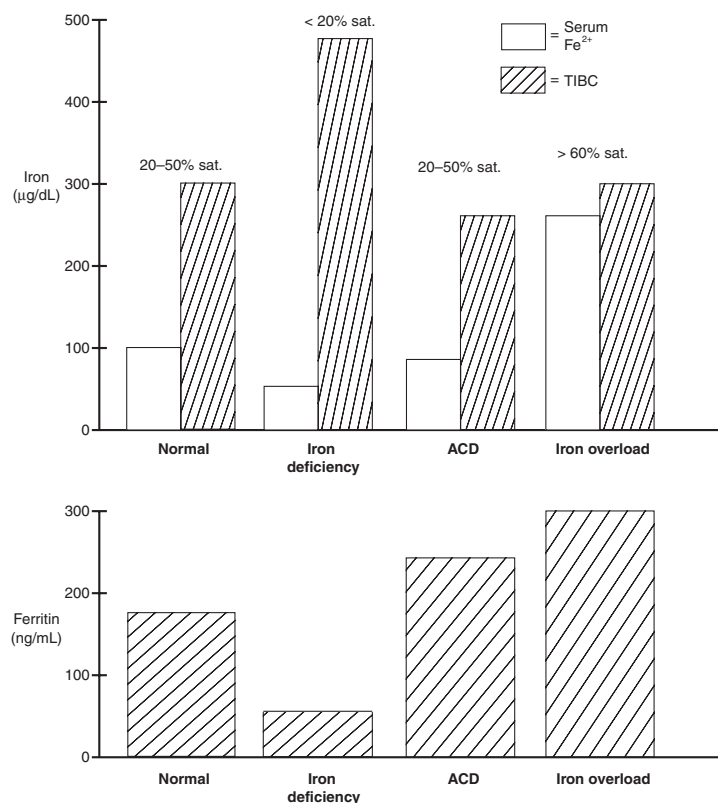
Normocytic,  
normochromic

### Etiology

Iron deficiency—↓ serum iron, ↑ TIBC, ↓ ferritin  
(see Color Image 20)  
Thalassemias—target cells (see Color Image 18)  
Lead poisoning, sideroblastic anemias  
Megaloblastic—vitamin B<sub>12</sub>/folate deficiency  
Drugs that block DNA synthesis (e.g., sulfa drugs, AZT)  
Marked reticulocytosis (bigger than mature RBCs)  
Acute hemorrhage  
Enzyme defects (e.g., G6PD deficiency, PK deficiency)  
RBC membrane defects (e.g., hereditary spherocytosis)  
Bone marrow disorders (e.g., aplastic anemia, leukemia)  
Hemoglobinopathies (e.g., sickle cell disease)  
Autoimmune hemolytic anemia  
Anemia of chronic disease (ACD)—↓ TIBC, ↑ ferritin,  
↑ storage iron in marrow macrophages

### Comments

Vitamin B<sub>12</sub> and folate deficiencies are associated with hypersegmented PMNs. Unlike folate deficiency, vitamin B<sub>12</sub> deficiency (e.g., pernicious anemia) is associated with neurologic problems.  
↓ serum haptoglobin and ↑ serum LDH indicate RBC hemolysis. Direct Coombs' test is used to distinguish between immune- vs. non-immune-mediated RBC hemolysis.



<b>Aplastic anemia</b>	Pancytopenia characterized by severe anemia, neutropenia, and thrombocytopenia caused by failure or destruction of multipotent myeloid stem cells, with inadequate production or release of differentiated cell lines.	
Causes	Radiation, benzene, chloramphenicol, alkylating agents, antimetabolites, viral agents (parvovirus B19, EBV, HIV), Fanconi's anemia, idiopathic (immune-mediated, 1° stem-cell defect). May follow acute hepatitis.	
Symptoms	Fatigue, malaise, pallor, purpura, mucosal bleeding, petechiae, infection.	
Pathologic features	Pancytopenia with normal cell morphology; hypocellular bone marrow with fatty infiltration. Diagnose with bone marrow biopsy.	
Treatment	Withdrawal of offending agent, allogenic bone marrow transplantation, RBC and platelet transfusion, G-CSF or GM-CSF.	

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<b>Blood dyscrasias</b>		
Sickle cell anemia	<p>HbS mutation is a single amino acid replacement in <math>\beta</math> chain (substitution of normal glutamic acid with valine). Low <math>O_2</math> or dehydration precipitates sickling. Heterozygotes (sickle cell trait) are relatively malaria resistant (balanced polymorphism). Complications in homozygotes (sickle cell disease) include aplastic crisis (due to parvovirus B19 infection), autosplenectomy, <math>\uparrow</math> risk of encapsulated organism infection, <i>Salmonella</i> osteomyelitis, painful crisis (vaso-occlusive), and splenic sequestration crisis (see Color Image 21). New therapies for sickle cell anemia include hydroxyurea (<math>\uparrow</math> HbF) and bone marrow transplantation.</p> <p>HbC defect is a different <math>\beta</math>-chain mutation; patients with HbC or HbSC (1 of each mutant gene) have milder disease than do HbSS patients.</p>	<p>8% of African-Americans carry the HbS trait; 0.2% have the disease.</p> <p>Sickled cells are crescent-shaped RBCs.</p> <p>“Crew cut” on skull x-ray due to marrow expansion from <math>\uparrow</math> erythropoiesis (also in thalassemias).</p>
$\alpha$ -thalassemia	<p>There are 4 <math>\alpha</math>-globin genes. In <math>\alpha</math>-thalassemia, the <math>\alpha</math>-globin chain is underproduced (as a function of number of bad genes, 1–4). There is no compensatory <math>\uparrow</math> of any other chains. HbH (<math>\beta_4</math>-tetramers, lacks 3 <math>\alpha</math>-globin genes). Hb Barts (<math>\gamma_4</math>-tetramers, lacks all 4 <math>\alpha</math>-globin genes) results in hydrops fetalis and intrauterine fetal death.</p>	<p><math>\alpha</math>-thalassemia is prevalent in Asia and Africa. <math>\beta</math>-thalassemia is prevalent in Mediterranean populations.</p>
$\beta$ -thalassemia	<p>In <math>\beta</math>-thalassemia minor (heterozygote), the <math>\beta</math> chain is underproduced; in <math>\beta</math>-thalassemia major (homozygote), the <math>\beta</math> chain is absent. In both cases, fetal hemoglobin production is compensatorily <math>\uparrow</math> but is inadequate. HbS/<math>\beta</math>-thalassemia heterozygote has mild to moderate disease (see Color Image 19).</p>	<p><math>\beta</math>-thalassemia major results in severe anemia requiring blood transfusions. Cardiac failure due to 2° hemochromatosis. Marrow expansion <math>\rightarrow</math> skeletal deformities.</p>

<b>Hemolytic anemias</b>		
	↑ serum bilirubin (jaundice, pigment gallstones), ↑ reticulocytes (marrow compensating for anemia).	
Autoimmune anemia	<p>Mostly extravascular hemolysis (accelerated RBC destruction in liver Kupffer cells and spleen).</p> <p><b>Warm</b> agglutinin (IgG)—chronic anemia seen in SLE, in CLL, or with certain drugs (e.g., α-methyl dopa).</p> <p><b>Cold</b> agglutinin (IgM)—acute anemia triggered by cold; seen during recovery from <i>Mycoplasma pneumoniae</i> or infectious mononucleosis.</p> <p>Erythroblastosis fetalis—seen in newborn due to Rh or other blood antigen incompatibility → mother's antibodies attack fetal RBCs.</p>	<p>Autoimmune hemolytic anemias are Coombs positive.</p> <p>Direct Coombs' test: anti-Ig Ab added to patient's RBCs agglutinate if RBCs are coated with Ig.</p> <p>Indirect Coombs' test: normal RBCs added to patient's serum agglutinate if serum has anti-RBC surface Ig.</p> <p><b>Warm</b> weather is GGGreat.</p> <p><b>Cold</b> ice cream . . . MMM.</p> <p>Coombs negative. Osmotic fragility test used to confirm.</p>
Hereditary spherocytosis	Intrinsic, extravascular hemolysis due to spectrin or ankyrin defect. RBCs are small and round with no central pallor → less membrane → ↑ MCHC, ↑ RDW.	
Paroxysmal nocturnal hemoglobinuria	Intravascular hemolysis due to membrane defect → ↑ sensitivity of RBCs to the lytic activity of complement.	↑ urine hemosiderin.
Microangiopathic anemia	Intravascular hemolysis seen in DIC, TTP/HUS, SLE, or malignant hypertension.	Schistocytes (helmet cells) seen on blood smear.
<b>DIC</b>		
	Activation of coagulation cascade leading to microthrombi and global consumption of platelets, fibrin, and coagulation factors.	
Causes	Sepsis (gram-negative), Trauma, Obstetric complications (most common), acute Pancreatitis, Malignancy, Nephrotic syndrome, Transfusion	<b>STOP Making New Thrombi!</b>
Lab findings	↑ PT, ↑ PTT, ↑ fibrin split products (D-dimers), ↓ platelet count. Helmet-shaped cells and schistocytes on blood smear.	
<b>Bleeding disorders</b>		
Platelet abnormalities	<p>Causes include:</p> <ol style="list-style-type: none"> <li>1. ITP (antiplatelet antibodies, ↑ megakaryocytes)</li> <li>2. TTP (schistocytes, ↑ LDH, neurologic and renal symptoms, fever, microangiopathic hemolytic anemia)</li> <li>3. DIC (schistocytes, ↑ fibrin split products)</li> <li>4. Aplastic anemia</li> <li>5. Drugs (e.g., immunosuppressive agents)</li> </ol>	Microhemorrhage: mucous membrane bleeding, epistaxis, petechiae, purpura, ↑ bleeding time.
Coagulation factor defects	<p>Coagulopathies include:</p> <ol style="list-style-type: none"> <li>1. Hemophilia A (factor VIII deficiency)</li> <li>2. Hemophilia B (factor IX deficiency)</li> <li>3. von Willebrand's disease (mild; most common bleeding disorder; deficiency of von Willebrand factor → defect of platelet adhesion and ↓ factor VIII survival)</li> </ol>	Macrohemorrhage: hemarthroses (bleeding into joints), easy bruising, ↑ PT and/or PTT.

**Hemorrhagic disorders**

Disorder	Platelet count <sup>b</sup>	Bleeding time	PT <sup>c</sup>	PTT <sup>d</sup>
Qualitative platelet defects <sup>a</sup>	—	↑	—	—
Thrombocytopenia	↓	↑	—	—
Hemophilia A or B	—	—	—	↑
von Willebrand's disease	—	↑	—	↑
DIC	↓	↑	↑	↑

<sup>a</sup>Bernard-Soulier disease = defect of platelet adhesion (↓ GP Ib); Glanzmann's thrombasthenia = defect of platelet aggregation (↓ GP IIb-IIIa).

<sup>b</sup>Note: platelet count must reach a very low value (15,000–20,000/mm<sup>3</sup>) before generalized bleeding occurs; thrombocytopenia = < 100,000/mm<sup>3</sup>.

<sup>c</sup>PT (extrinsic)—factors II, V, VII, and X.

<sup>d</sup>PTT (intrinsic)—all factors except VII.

**Lymphomas****Hodgkin's**

Presence of Reed-Sternberg cells (RS cells are CD30<sup>+</sup> and CD15<sup>+</sup> B-cell origin) (see Color Image 25)  
 Localized, single group of nodes; extranodal rare; contiguous spread  
 Constitutional ("B") signs/symptoms—low-grade fever, night sweats, weight loss  
 Mediastinal lymphadenopathy  
 50% of cases associated with EBV; bimodal distribution—young and old; more common in men except for nodular sclerosing type  
 Good prognosis = ↑ lymphocytes, ↓ RS

**Non-Hodgkin's**

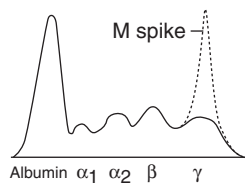
Associated with HIV and immunosuppression  
 Multiple, peripheral nodes; extranodal involvement common; noncontiguous spread  
 Majority involve B cells (except those of lymphoblastic T-cell origin)  
 No hypergammaglobulinemia  
 Fewer constitutional signs/symptoms  
 Peak incidence 20–40 years old

**Hodgkin's lymphoma**

Type	RS	Lymphos	Prognosis	Comments
Nodular sclerosing (65–75%)	+	+++	Excellent	Most common; collagen banding; lacunar cells; women > men; primarily young adults.
Mixed cellularity (25%)	++++	+++	Intermediate	Numerous RS cells.
Lymphocyte predominant (6%)	+	++++	Excellent	< 35-year-old males.
Lymphocyte depleted (rare)	*	+	Poor	Older males with disseminated disease.

\*RS high relative to lymphocytes

### Multiple myeloma



(Adapted, with permission, from Stobo J et al. *The Principles and Practice of Medicine*, 23rd ed. Stamford, CT: Appleton & Lange, 1996:806.)

Monoclonal plasma cell (“fried-egg” appearance) cancer that arises in the marrow and produces large amounts of IgG (55%) or IgA (25%). Most common 1° tumor arising within bone in adults. Destructive bone lesions and consequent hypercalcemia. Renal insufficiency, ↑ susceptibility to infection, and anemia. Associated with 1° amyloidosis and punched-out lytic bone lesions on x-ray. Characterized by monoclonal immunoglobulin spike (M protein) on serum protein electrophoresis and Ig light chains in urine (Bence Jones protein). Blood smear shows RBCs stacked like poker chips (rouleau formation). Compare with Waldenström’s macroglobulinemia → M spike = IgM (→ hyperviscosity symptoms); no lytic bone lesions (see Color Image 23).

### Reed-Sternberg cells

Distinctive tumor giant cell seen in Hodgkin’s disease; binucleate or bilobed with the 2 halves as mirror images (“owl’s eyes”). Necessary but not sufficient for a diagnosis of Hodgkin’s disease. Variants include lacunar cells in nodular sclerosis variant.

### Non-Hodgkin’s lymphoma

Type	Occurs in	Cell type	Genetics	Comments
Small lymphocytic lymphoma	Adults	B cells		Like CLL with focal mass; low grade.
Follicular lymphoma (small cleaved cell)	Adults	B cells	t(14;18) <i>bcl-2</i> expression	Most common (adult). Difficult to cure; indolent course; <i>bcl-2</i> is involved in apoptosis.
Diffuse large cell	Usually older adults, but 20% occur in children	80% B cells 20% T cells (mature)		Aggressive, but up to 50% are curable.
Mantle cell lymphoma	Adults	B cells	t(11;14)	Poor prognosis, CD5+
Lymphoblastic lymphoma	Most often children	T cells (immature)		Most common in children; commonly presents with ALL and mediastinal mass; very aggressive T-cell lymphoma.
Burkitt’s lymphoma	Most often children	B cells	t(8;14) <i>c-myc</i> gene moves next to heavy-chain Ig gene (14)	“Starry-sky” appearance (sheets of lymphocytes with interspersed macrophages); associated with EBV; jaw lesion in endemic form in Africa; pelvis or abdomen in sporadic form (see Color Image 24).

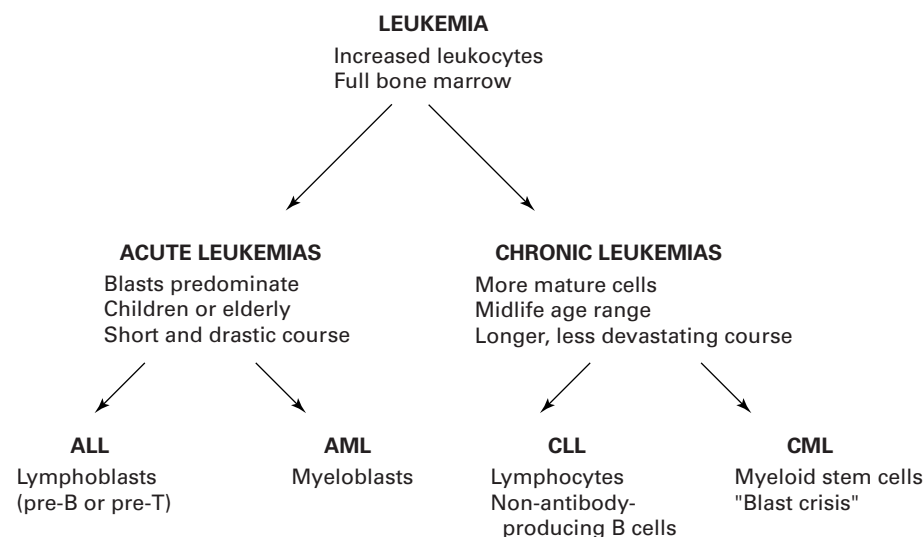
**Chromosomal translocations**

Translocation	Associated disorder
t(9;22) (Philadelphia chromosome)	CML ( <i>bcr-abl</i> hybrid)
t(8;14)	Burkitt's lymphoma ( <i>c-myc</i> activation)
t(14;18)	Follicular lymphomas ( <i>bcl-2</i> activation)
t(15;17)	M3 type of AML (responsive to all- <i>trans</i> retinoic acid)
t(11;22)	Ewing's sarcoma
t(11;14)	Mantle cell lymphoma

**Leukemias**

General considerations—↑ number of circulating leukocytes in blood; bone marrow infiltrates of leukemic cells; marrow failure can cause anemia (↓ RBCs), infections (↓ mature WBCs), and hemorrhage (↓ platelets); leukemic cell infiltrates in liver, spleen, and lymph nodes are common (see Color Image 22).

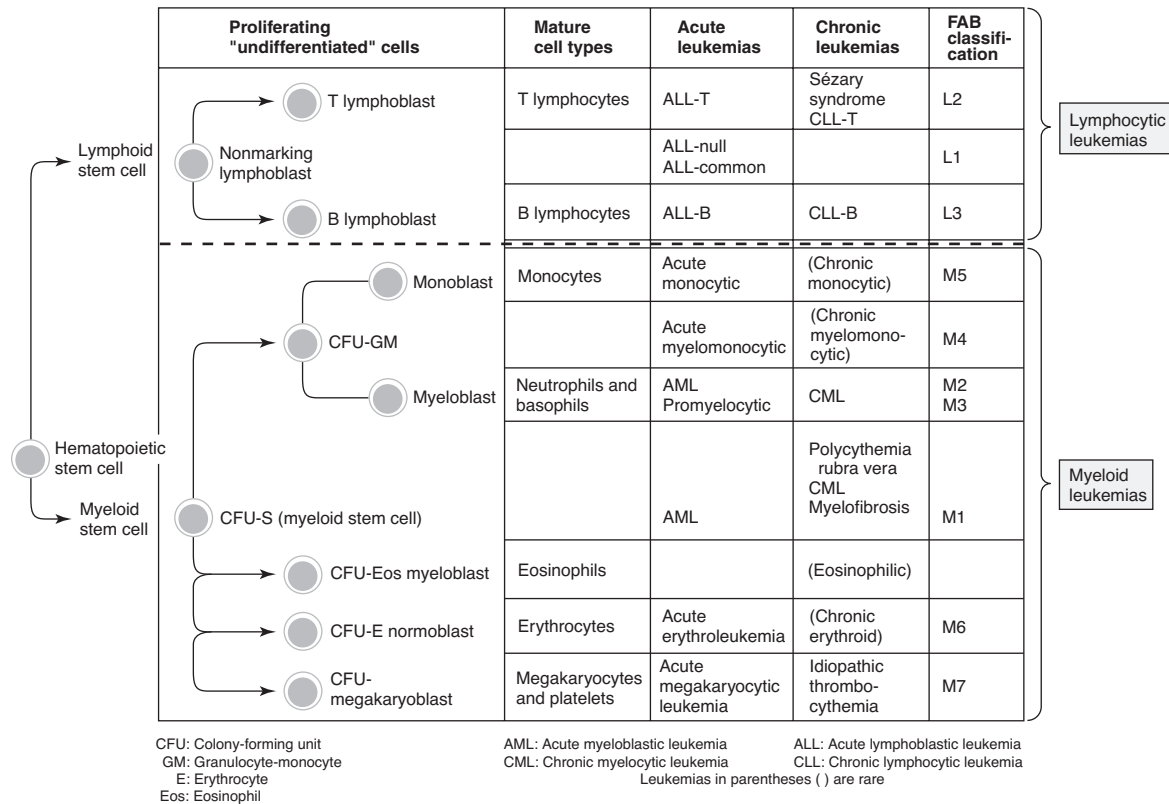
ALL	Children; lymphoblasts; most responsive to therapy. May spread to CNS and testes.
AML	Auer rods; myeloblasts; adults.
CLL	Older adults; lymphadenopathy; hepatosplenomegaly; few symptoms; indolent course; ↑ smudge cells in peripheral blood smear; warm antibody autoimmune hemolytic anemia; very similar to SLL (small lymphocytic lymphoma).
CML	Most commonly associated with Philadelphia chromosome (t[9;22], <i>bcr-abl</i> ); myeloid stem cell proliferation; presents with ↑ neutrophils and metamyelocytes; splenomegaly; may accelerate to AML ("blast crisis"). Very low leukocyte alkaline phosphatase (vs. leukemoid reaction).

**Auer bodies (rods)**

Auer rods are peroxidase-positive cytoplasmic inclusions in granulocytes and myeloblasts. Primarily seen in acute promyelocytic leukemia (M3). Treatment of AML M3 can release Auer rods → DIC.



## Leukemia classification



(Adapted, with permission, from Chandrasoma P, Taylor CE. *Concise Pathology*, 3rd ed. Stamford, CT: Appleton & Lange, 1998:410.)

## Histiocytosis X

Caused by Langerhans' cells from the monocyte lineage that infiltrate the lung. Primarily affects young adults. Worse with smoking.

## Heparin

Mechanism	Catalyzes the activation of antithrombin III, ↓ thrombin and Xa. Short half-life.
Clinical use	Immediate anticoagulation for pulmonary embolism, stroke, angina, MI, DVT. Used during pregnancy (does not cross placenta). Follow PTT.
Toxicity	Bleeding, thrombocytopenia, drug-drug interactions. For rapid reversal of heparinization, use <b>protamine sulfate</b> (positively charged molecule that acts by binding negatively charged heparin).
Note	Newer <b>low-molecular-weight heparins</b> (enoxaparin) act more on Xa, have better bioavailability and 2–4 times longer half-life. Can be administered subcutaneously and without laboratory monitoring. Not easily reversible.

**Warfarin (Coumadin)**

Mechanism	Interferes with normal synthesis and $\gamma$ -carboxylation of vitamin K–dependent clotting factors II, VII, IX, and X and protein C and S. Affects <b>EX</b> trinsic pathway and $\uparrow$ <b>PT</b> . Long half-life.	The <b>EX</b> - <b>Pa</b> Triot went to <b>WAR</b> (farin).
Clinical use	Chronic anticoagulation. Not used in pregnant women (because warfarin, unlike heparin, can cross the placenta). Follow PT values.	
Toxicity	Bleeding, teratogenic, drug-drug interactions.	

**Heparin vs. warfarin**

	<b>Heparin</b>	<b>Warfarin</b>
Structure	Large anionic polymer, acidic	Small lipid-soluble molecule
Route of administration	Parenteral (IV, SC)	Oral
Site of action	Blood	Liver
Onset of action	Rapid (seconds)	Slow, limited by half-lives of normal clotting factors
Mechanism of action	Activates antithrombin III, which $\downarrow$ the action of IIa (thrombin) and Xa	Impairs the synthesis of vitamin K–dependent clotting factors II, VII, IX, and X (vitamin K antagonist)
Duration of action	Acute (hours)	Chronic (weeks or months)
Inhibits coagulation in vitro	Yes	No
Treatment of acute overdose	Protamine sulfate	IV vitamin K and fresh frozen plasma
Monitoring	PTT (intrinsic pathway)	PT (extrinsic pathway)
Crosses placenta	No	Yes (teratogenic)

## Thrombolytics

Mechanism

Clinical use

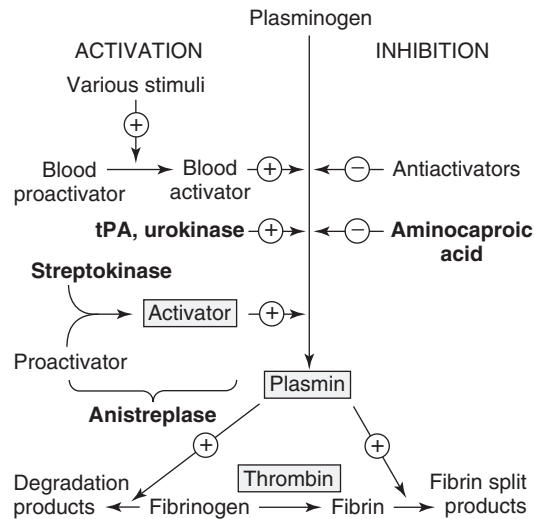
Toxicity

Streptokinase, urokinase, tPA (alteplase), APSAC (anistreplase).

Directly or indirectly aid conversion of plasminogen to plasmin, the major fibrinolytic enzyme, which cleaves thrombin and fibrin clots.

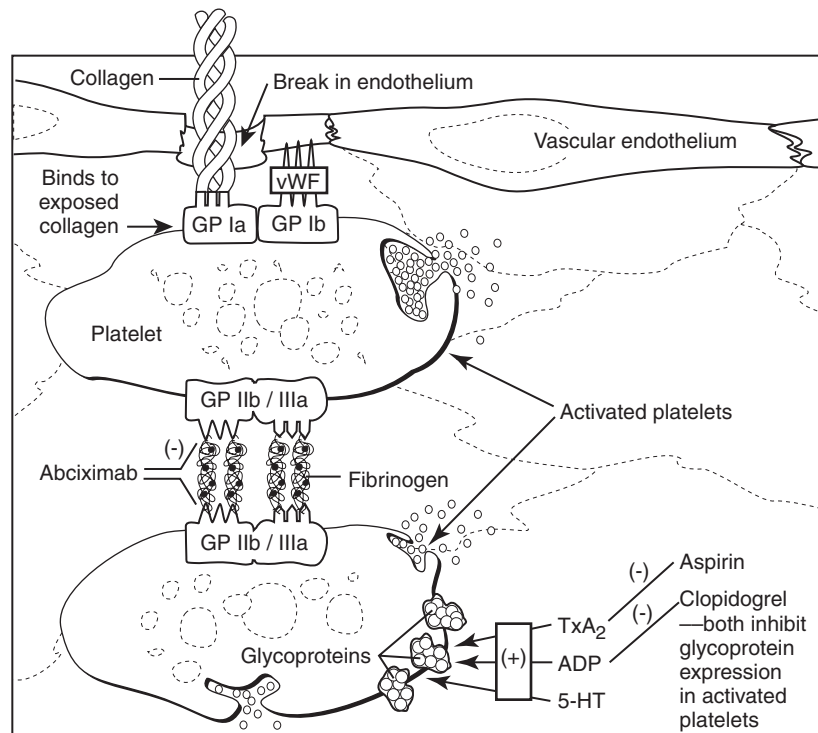
Early MI, early ischemic stroke.

Bleeding. Contraindicated in patients with active bleeding, history of intracranial bleeding, recent surgery, known bleeding diathesis, or severe hypertension. Treat toxicity with aminocaproic acid, an inhibitor of fibrinolysis.



(Adapted, with permission, from Katzung BG. *Basic and Clinical Pharmacology*, 7th ed. Stamford, CT: Appleton & Lange, 1997:550.)

## Mechanism of antiplatelet interaction



**Aspirin (ASA)**

Mechanism	Acetylates and irreversibly inhibits cyclooxygenase (both COX-1 and COX-2) to prevent conversion of arachidonic acid to prostaglandins. ↑ bleeding time. No effect on PT, PTT.
Clinical use	Antipyretic, analgesic, anti-inflammatory, antiplatelet drug.
Toxicity	Gastric ulceration, bleeding, hyperventilation, Reye's syndrome, tinnitus (CN VIII).

**Clopidogrel, ticlopidine**

Mechanism	Inhibit platelet aggregation by irreversibly blocking ADP receptors. Inhibit fibrinogen binding by preventing glycoprotein IIb/IIIa expression.
Clinical use	Acute coronary syndrome; coronary stenting. ↓ incidence or recurrence of thrombotic stroke.
Toxicity	Neutropenia (ticlopidine).

**Abciximab**

Mechanism	Monoclonal antibody that binds to the glycoprotein receptor IIb/IIIa on activated platelets, preventing aggregation.
Clinical use	Acute coronary syndromes, percutaneous transluminal coronary angioplasty.
Toxicity	Bleeding, thrombocytopenia.

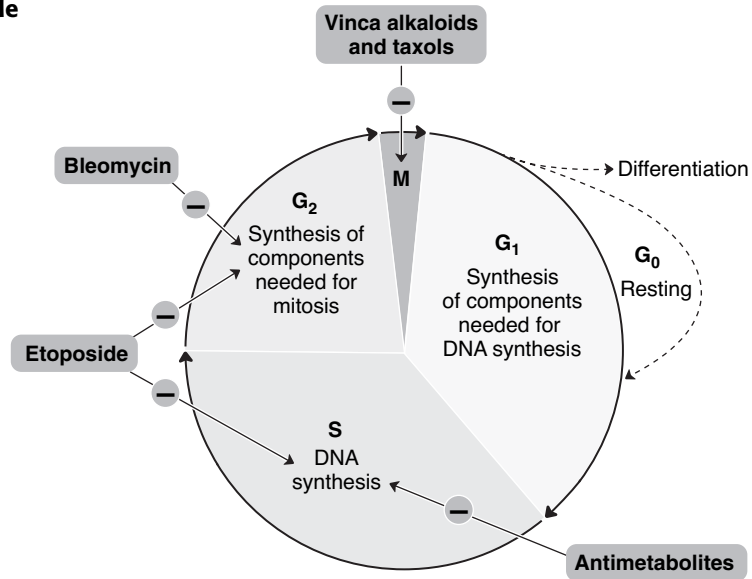
**Cancer drugs—site of action****Nucleotide synthesis****DNA****mRNA****Protein**

1. Methotrexate + 5-FU—↓ thymidine synthesis
2. 6-MP—↓ purine synthesis
3. Cytarabine
4. Alkylating agents + cisplatin—DNA cross-linkage
5. Dactinomycin + doxorubicin—DNA intercalation
6. Bleomycin—strand breakage + DNA intercalation
7. Etoposide—strand breakage
8. Steroids
9. Tamoxifen
10. Vinca alkaloids—inhibit microtubule formation
11. Paclitaxel—inhibits microtubule disassembly

Cell cycle specific—  
antimetabolites (MTX, 5-FU, 6-MP), etoposide, bleomycin, vinca alkaloids, paclitaxel.

Cell cycle nonspecific—  
alkylating agents, antibiotics (dactinomycin, doxorubicin, bleomycin).

## Cancer drugs—cell cycle



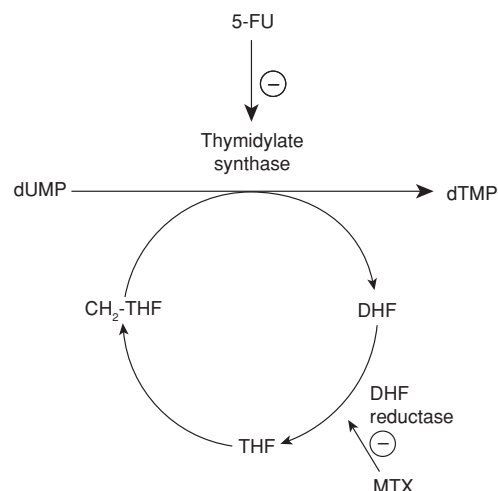
(Adapted, with permission, from Katzung BG, Trevor AJ. *USMLE Road Map: Pharmacology*, 1st ed. New York: McGraw-Hill, 2003:133.)

### Methotrexate (MTX)

Mechanism	S-phase-specific antimetabolite. Folic acid analog that inhibits dihydrofolate reductase, resulting in ↓ dTMP and therefore ↓ DNA and protein synthesis.
Clinical use	Leukemias, lymphomas, choriocarcinoma, sarcomas. Abortion, ectopic pregnancy, rheumatoid arthritis, psoriasis.
Toxicity	Myelosuppression, which is reversible with leucovorin (folinic acid) “rescue.” Macrovesicular fatty change in liver.

### 5-fluorouracil (5-FU)

Mechanism	S-phase-specific antimetabolite. Pyrimidine analog bioactivated to 5F-dUMP, which covalently complexes folic acid. This complex inhibits thymidylate synthase, resulting in ↓ dTMP and same effects as MTX.
Clinical use	Colon cancer and other solid tumors, basal cell carcinoma (topical). Synergy with MTX.
Toxicity	Myelosuppression, which is NOT reversible with leucovorin; photosensitivity. Can “rescue” with thymidine.



**6-mercaptopurine (6-MP)**

Mechanism	Blocks de novo purine synthesis. Activated by HGPRTase.
Clinical use	Leukemias, lymphomas (not CLL or Hodgkin's).
Toxicity	Bone marrow, GI, liver. Metabolized by xanthine oxidase; thus ↑ toxicity with allopurinol.

**Cytarabine (ara-C)**

Mechanism	Inhibits DNA polymerase.
Clinical use	AML.
Toxicity	Leukopenia, thrombocytopenia, megaloblastic anemia.

**Cyclophosphamide, ifosfamide**

Mechanism	Alkylating agents; covalently x-link (interstrand) DNA at guanine N-7. Require bioactivation by liver.
Clinical use	Non-Hodgkin's lymphoma, breast and ovarian carcinomas. Also immunosuppressants.
Toxicity	Myelosuppression; hemorrhagic cystitis, which can be partially prevented with mesna.

**Nitrosoureas**

Mechanism	Carmustine, lomustine, semustine, streptozocin.
Clinical use	Alkylate DNA. Require bioactivation. Cross blood-brain barrier → CNS.
Toxicity	Brain tumors (including glioblastoma multiforme). CNS toxicity (dizziness, ataxia).

**Cisplatin, carboplatin**

Mechanism	Act like alkylating agents.
Clinical use	Testicular, bladder, ovary, and lung carcinomas.
Toxicity	Nephrotoxicity and acoustic nerve damage.

**Busulfan**

Mechanism	Alkylates DNA.
Clinical use	CML.
Toxicity	Pulmonary fibrosis, hyperpigmentation.

**Doxorubicin (Adriamycin), daunorubicin**

Mechanism	Generate free radicals and noncovalently intercalate in DNA (creating breaks in DNA strand to ↓ replication).
Clinical use	Part of the ABVD combination regimen for Hodgkin's and for myelomas, sarcomas, and solid tumors (breast, ovary, lung).
Toxicity	Cardiotoxicity; also myelosuppression and marked alopecia. Toxic extravasation.

**Dactinomycin (actinomycin D)**

Mechanism	Intercalates in DNA.	ACTinomycin D is used for childhood tumors (children ACT out).
Clinical use	Wilms' tumor, Ewing's sarcoma, rhabdomyosarcoma.	
Toxicity	Myelosuppression.	

**Bleomycin**

Mechanism	Induces formation of free radicals, which cause breaks in DNA strands.
Clinical use	Testicular cancer, lymphomas (part of the ABVD regimen for Hodgkin's).
Toxicity	Pulmonary fibrosis, skin changes, but minimal myelosuppression.

**Etoposide (VP-16)**

Mechanism	G <sub>2</sub> -phase-specific agent that inhibits topoisomerase II and ↑ DNA degradation.
Clinical use	Small cell carcinoma of the lung and prostate, testicular carcinoma.
Toxicity	Myelosuppression, GI irritation, alopecia.

**Prednisone**

Mechanism	May trigger apoptosis. May even work on nondividing cells.
Clinical use	Most commonly used glucocorticoid in cancer chemotherapy. Used in CLL, Hodgkin's lymphomas (part of the MOPP regimen). Also an immunosuppressant used in autoimmune diseases.
Toxicity	Cushing-like symptoms; immunosuppression, cataracts, acne, osteoporosis, hypertension, peptic ulcers, hyperglycemia, psychosis.

**Tamoxifen, raloxifene**

Mechanism	Receptor antagonists in breast, agonists in bone; block the binding of estrogen to estrogen receptor-positive cells.
Clinical use	Breast cancer. Also useful to prevent osteoporosis.
Toxicity	Tamoxifen may ↑ the risk of endometrial carcinoma via partial agonist effects; "hot flashes." Raloxifene does not cause endometrial carcinoma because it is an endometrial antagonist.

**Trastuzumab (Herceptin)**

Mechanism	Monoclonal antibody against HER-2 ( <i>erb-B2</i> ). Helps kill breast cancer cells that overexpress HER-2, possibly through antibody-dependent cytotoxicity.
Clinical use	Metastatic breast cancer.
Toxicity	Cardiotoxicity.

**Imatinib (Gleevec)**

Mechanism	Philadelphia chromosome <i>bcr-abl</i> tyrosine kinase inhibitor.
Clinical use	CML, GI stromal tumors.
Toxicity	Fluid retention.

**Vincristine, vinblastine**

Mechanism	M-phase-specific alkaloids that bind to tubulin and block polymerization of microtubules so that mitotic spindle cannot form.
Clinical use	Part of the MOPP (Oncovin [vincristine]) regimen for lymphoma, Wilms' tumor, choriocarcinoma.
Toxicity	Vincristine—neurotoxicity (areflexia, peripheral neuritis), paralytic ileus. VinBLASTine BLASTs Bone marrow (suppression).

**Paclitaxel, other taxols**

Mechanism	M-phase-specific agents that bind to tubulin and hyperstabilize polymerized microtubules so that mitotic spindle cannot break down (anaphase cannot occur).
Clinical use	Ovarian and breast carcinomas.
Toxicity	Myelosuppression and hypersensitivity.

# Musculoskeletal and Connective Tissue

*“I just use my muscles like a conversation piece, like someone walking a cheetah down 42nd Street.”*

—Arnold Schwarzenegger

*“There’s 215 bones in the human body. That’s one.”*

—Sarah Connor in *Terminator 2: Judgment Day*

- ▶ High-Yield Clinical Vignettes
- ▶ Anatomy
- ▶ Physiology
- ▶ Pathology
- ▶ Pharmacology

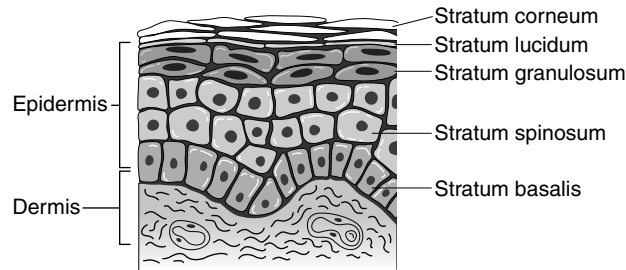


- |                                                                                                                                                                                                 |                                                                      |                                                                   |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------|-------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>■ Soccer player who was kicked in the leg suffered a damaged medial meniscus.</li> </ul>                                                                 | <p>What else is likely to have been damaged?</p>                     | <p>Anterior cruciate ligament (remember the “unhappy triad”).</p> |
| <ul style="list-style-type: none"> <li>■ Gymnast dislocates her shoulder anteriorly.</li> </ul>                                                                                                 | <p>What nerve is most likely to have been damaged?</p>               | <p>Axillary nerve (C5, C6).</p>                                   |
| <ul style="list-style-type: none"> <li>■ X-ray shows bilateral hilar lymphadenopathy.</li> </ul>                                                                                                | <p>What is the diagnosis?</p>                                        | <p>Sarcoidosis.</p>                                               |
| <ul style="list-style-type: none"> <li>■ Child exhibits weakness and enlarged calves.</li> </ul>                                                                                                | <p>What is the disease, and how it is inherited?</p>                 | <p>Duchenne’s muscular dystrophy; X-linked recessive.</p>         |
| <ul style="list-style-type: none"> <li>■ 25-year-old woman presents with a low-grade fever, a rash across her nose that gets worse when she is out in the sun, and widespread edema.</li> </ul> | <p>You are concerned about what disease?</p>                         | <p>SLE.</p>                                                       |
| <ul style="list-style-type: none"> <li>■ 85-year-old man presents with acute knee pain and swelling. X-ray shows joint space without erosion.</li> </ul>                                        | <p>What is the diagnosis, and what would you find on aspiration?</p> | <p>Pseudogout; rhomboid calcium pyrophosphate crystals.</p>       |

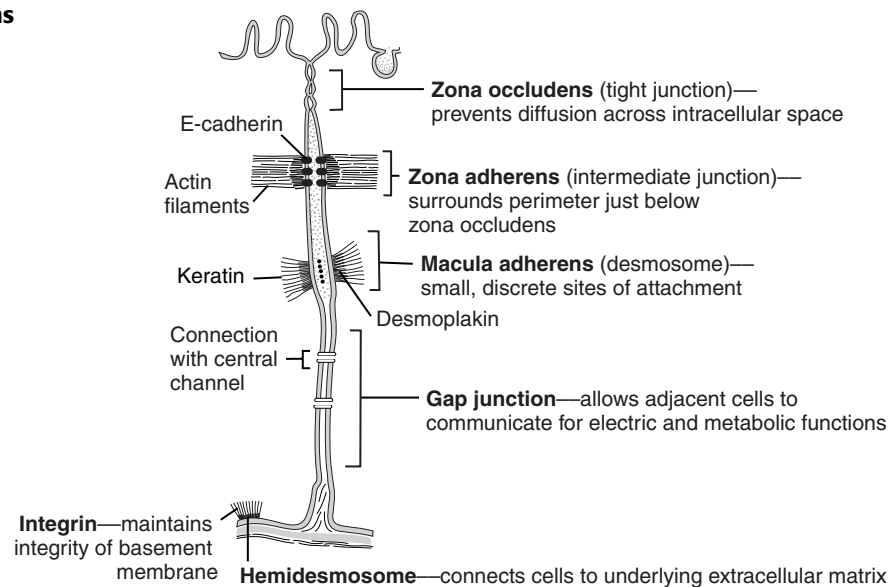
## Epidermis layers

From surface to base: stratum Corneum, stratum Lucidum, stratum Granulosum, stratum Spinosum, stratum Basalis.

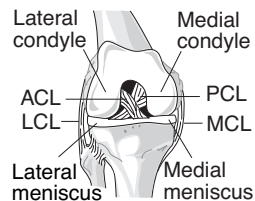
Californians Like Girls in String Bikinis.



## Epithelial cell junctions



## Unhappy triad/ knee injury



This common football injury (caused by clipping from the lateral side) consists of damage to medial collateral ligament (MCL), medial meniscus, and anterior cruciate ligament (ACL).

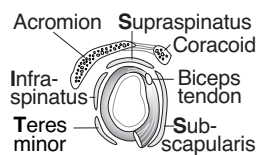
PCL = posterior cruciate ligament. LCL = lateral collateral ligament.

“Anterior” and “posterior” in ACL and PCL refer to sites of **tibial** attachment.

Positive anterior drawer sign indicates tearing of the ACL.

Abnormal passive abduction indicates a torn MCL.

## Rotator cuff muscles



Shoulder muscles that form the rotator cuff:

**Supraspinatus**—helps deltoid abduct arm.

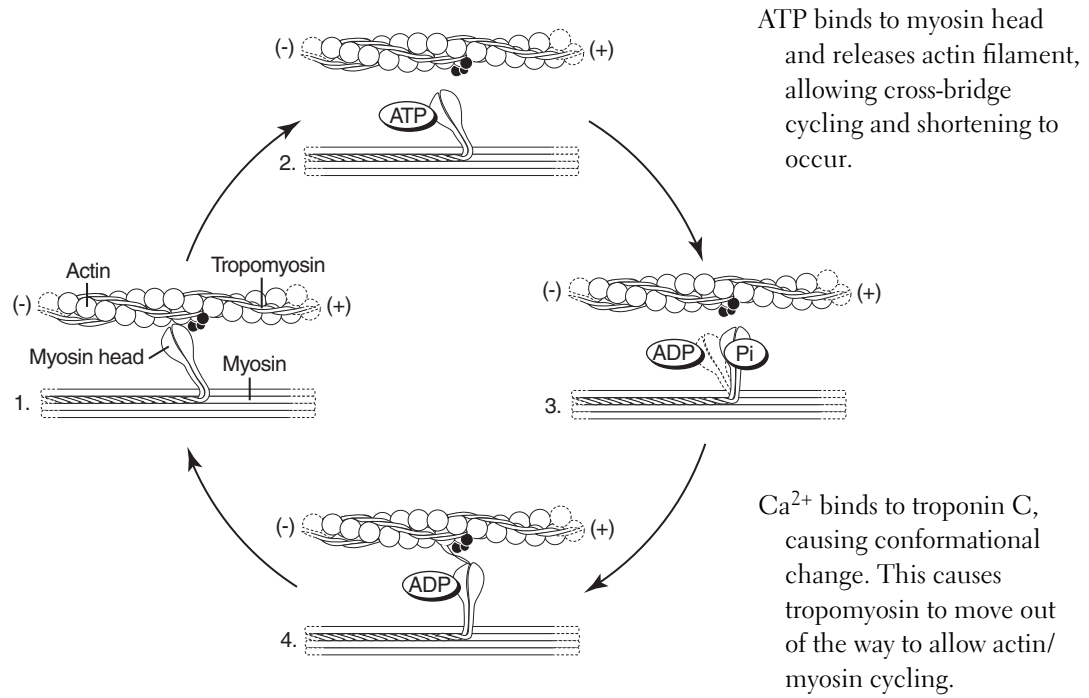
**Infraspinatus**—laterally rotates arm.

**Teres minor**—adducts and laterally rotates arm.

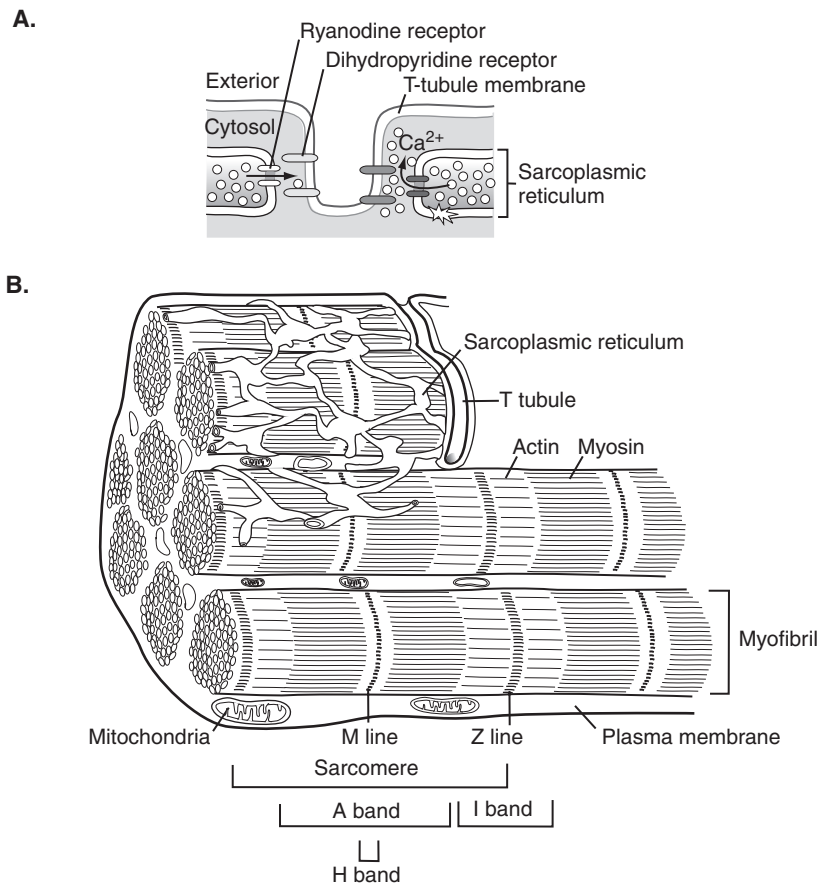
**Subscapularis**—medially rotates and adducts arm.

**S I t S** (small t is for teres minor).

### Skeletal muscle contraction



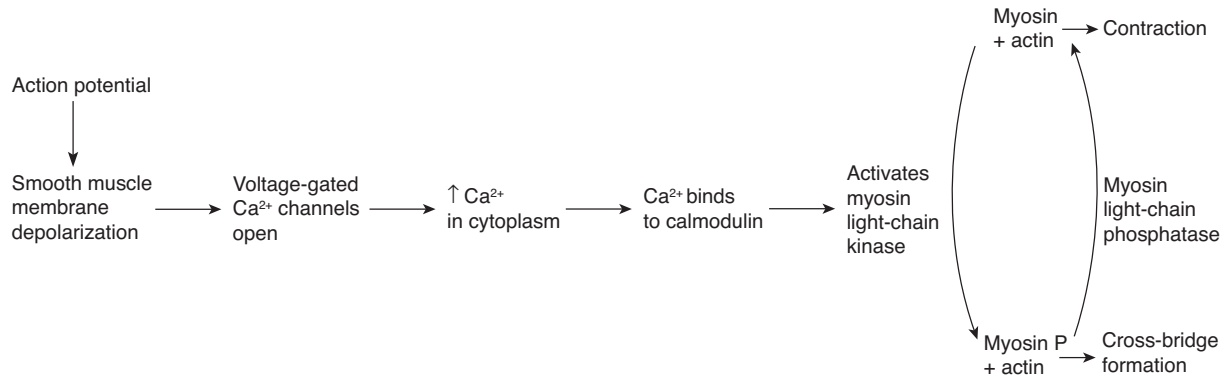
## Muscle conduction to contraction



### Action potential:

1. Action potential depolarization opens voltage-gated  $\text{Ca}^{2+}$  channels, inducing neurotransmitter release.
2. Postsynaptic ligand binding leads to muscle cell depolarization in the motor end plate.
3. Depolarization travels along muscle cell and down the T tubule.
4. Depolarization of the voltage-sensitive dihydropyridine receptor, coupled to the ryanodine receptor on the sarcoplasmic reticulum, induces a conformational change causing  $\text{Ca}^{2+}$  release.
5. Released  $\text{Ca}^{2+}$  binds to troponin C, causing a conformational change that moves tropomyosin out of the myosin-binding groove on actin filaments.
6. Myosin releases bound ADP and is displaced on the actin filament (power stroke).  
Contraction results in H and I band shortening, but the A band remains the same length.

### Smooth muscle contraction



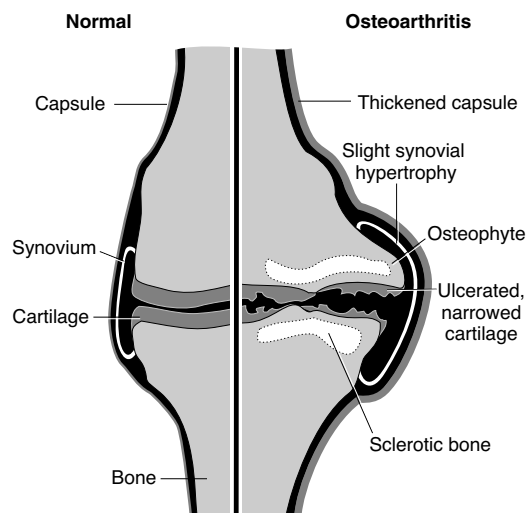
► MUSCULOSKELETAL AND CONNECTIVE TISSUE—PATHOLOGY

### Achondroplasia

Autosomal-dominant trait. Failure of longitudinal bone growth → short limbs. Membranous ossification is not affected (skull, facial bones, and axial skeleton are normal). Impaired cartilage maturation in growth plate caused by fibroblast growth factor receptor mutation.

### Osteoarthritis

Mechanical—wear and tear of joints leads to destruction of articular cartilage, subchondral cysts, sclerosis, osteophytes, eburnation, Heberden's nodes (DIP), and Bouchard's nodes (PIP).  
Predisposing factors: age, obesity, joint deformity.  
Classic presentation: pain in weight-bearing joints after use (e.g., at the end of the day), improving with rest. No systemic symptoms.



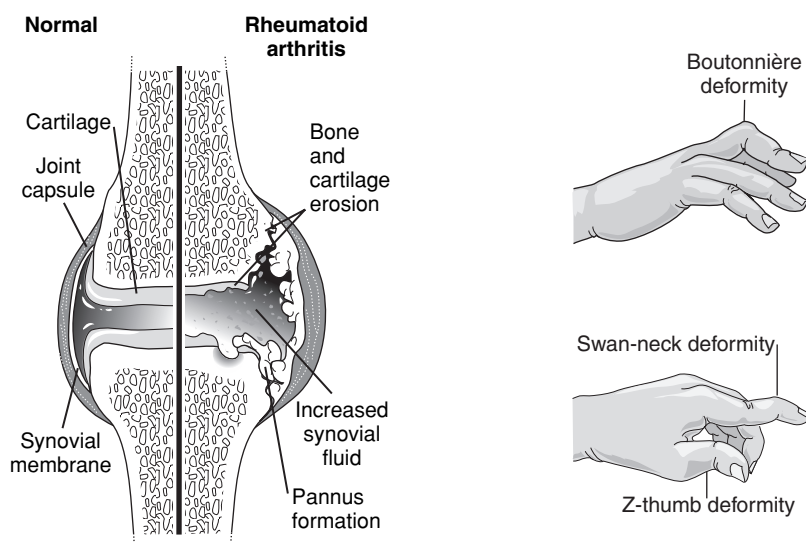
(Adapted, with permission, from Stobo J et al. *The Principles and Practice of Medicine*, 23rd ed. Stamford, CT: Appleton & Lange, 1996:241.)

## Rheumatoid arthritis

Autoimmune—inflammatory disorder affecting synovial joints, with pannus formation in joints (MCP, PIP), subcutaneous rheumatoid nodules, ulnar deviation, subluxation (see Color Image 56).

Females > males. 80% of RA patients have positive rheumatoid factor (anti-IgG antibody).

Classic presentation: morning stiffness improving with use, symmetric joint involvement, and systemic symptoms (fever, fatigue, pleuritis, pericarditis).



## Osteoporosis

### Type I

Reduction of bone mass in spite of normal bone mineralization. Sparse trabeculae.

Postmenopausal; ↑ bone resorption due to ↓ estrogen levels. Estrogen replacement is controversial as prophylaxis (side effects).

### Type II

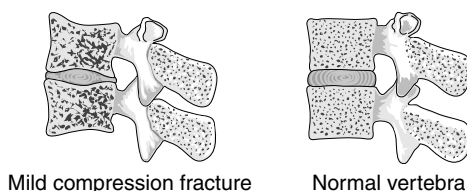
Senile osteoporosis—affects men and women > 70 years.

Affects whites > blacks > Asians.

Vertebral crush fractures—acute back pain, loss of height, kyphosis.

Distal radius (Colles') fractures, vertebral wedge fractures.

Bisphosphonates or pulsatile PTH for severe cases.



## Osteopetrosis (marble bone disease)

Failure of normal bone resorption → thickened, dense bones. Bone defect is due to abnormal function of osteoclasts. Serum calcium, phosphate, and **alkaline phosphatase** are **normal**. Decreased marrow space leads to anemia, thrombocytopenia, infection.

## Osteomalacia/rickets

Defective mineralization of osteoid → soft bones. Vitamin D deficiency in adults → ↓ calcium levels → ↑ secretion of PTH, ↓ in serum phosphate. Reversible when vitamin D is replaced. Vitamin D deficiency in childhood causes rickets.

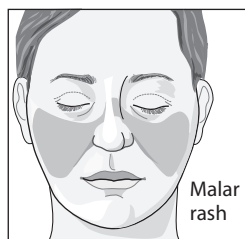
## Osteitis fibrosa cystica

Caused by hyperparathyroidism. Characterized by “brown tumors” (cystic spaces lined by osteoclasts, filled with fibrous stroma and sometimes blood). High serum calcium, low serum phosphorus, and high alkaline phosphatase.

► **MUSCULOSKELETAL AND CONNECTIVE TISSUE—PATHOLOGY (continued)**

<b>Paget's disease (osteitis deformans)</b>	Abnormal bone architecture caused by ↑ in both osteoblastic and osteoclastic activity. Serum calcium, phosphorus, and PTH levels are normal. Serum <b>alkaline phosphatase</b> is <b>elevated</b> . Long bone chalkstick fractures. Increased blood flow may cause high output CHF.	
<b>Polyostotic fibrous dysplasia</b>	Bone is replaced by fibroblasts, collagen, and irregular bony trabeculae. Affects many bones. <b>Albright's syndrome</b> is a form of polyostotic fibrous dysplasia in which there are multiple unilateral bone lesions associated with endocrine abnormalities (precocious puberty) and unilateral pigmented skin lesions.	
<b>Polymyalgia rheumatica</b>	Pain and stiffness in shoulders and hips, often with fever, malaise, and weight loss. Does not cause muscular weakness. ↑ ESR. Occurs in patients > 50 years of age; associated with temporal (giant cell) arteritis. Treated with prednisone.	
<b>Polymyositis/ dermatomyositis</b>	<p><b>Polymyositis</b>—progressive symmetric proximal muscle weakness caused by CD8<sup>+</sup> T-cell-induced injury to myofibers. Muscle biopsy with evidence of inflammation is diagnostic.</p> <p><b>Dermatomyositis</b>—similar to polymyositis but also involves "shawl and face" skin rash and ↑ risk of malignancy.</p> <p>Labs for polymyositis/dermatomyositis show ↑ CK, ↑ aldolase, and positive ANA, anti-Jo-1.</p>	
<b>Mixed connective tissue disease</b>	Raynaud's phenomenon, arthralgias, myalgias, fatigue, and esophageal hypomotility. Antibodies to U1RNP. Responds to steroids.	
<b>Sjögren's syndrome</b>	Classic triad—xerophthalmia (dry eyes, conjunctivitis), xerostomia (dry mouth, dysphagia), arthritis. Parotid enlargement, ↑ risk of B-cell lymphoma, dental caries. Autoantibodies to ribonucleoprotein antigens, SS-A (Ro), SS-B (La). Predominantly affects <b>females</b> between 40 and 60 years of age.	<p>Associated with rheumatoid arthritis.</p> <p>Sicca syndrome—dry eyes, dry mouth, nasal and vaginal dryness, chronic bronchitis, reflux esophagitis.</p>

### Systemic lupus erythematosus



90% are female and between ages 14 and 45. Most common and severe in black females. Symptoms include fever, fatigue, weight loss, nonbacterial verrucous endocarditis, hilar adenopathy, and Raynaud's phenomenon. **Wire loop** lesions in kidney with immune complex deposition (with nephrotic syndrome); death from renal failure and infections. False positives on syphilis tests (RPR/VDRL) due to antiphospholipid antibodies.

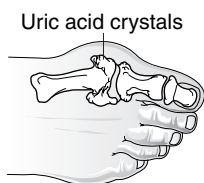
Lab tests detect presence of:

1. Antinuclear antibodies (ANA)—sensitive, but not specific for SLE
2. Antibodies to double-stranded DNA (anti-dsDNA)—very specific, poor prognosis
3. Anti-Smith antibodies (anti-Sm)—very specific, but not prognostic
4. Antihistone antibodies—drug-induced lupus (see Color Image 52)

### I'M DAMN SHARP:

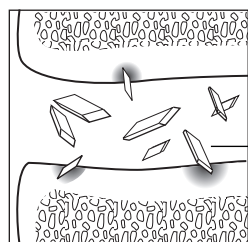
Immunoglobulins  
(anti-dsDNA, anti-Sm,  
antiphospholipid)  
Malar rash  
Discoid rash  
Antinuclear antibody  
Mucositis (oropharyngeal  
ulcers)  
Neurologic disorders  
Serositis (pleuritis,  
pericarditis)  
Hematologic disorders  
Arthritis  
Renal disorders  
Photosensitivity

### Gout



Precipitation of monosodium urate crystals into joints due to hyperuricemia, which can be caused by Lesch-Nyhan syndrome, PRPP excess, ↓ excretion of uric acid, or glucose-6-phosphatase deficiency. Also associated with the use of thiazide diuretics, which competitively inhibit the secretion of uric acid. Asymmetric joint distribution. Classic manifestation is painful MTP joint in the big toe (podagra). Tophus formation (often on external ear or Achilles tendon). Crystals are needle shaped and **negatively birefringent**. More common in men. Acute attack tends to occur after alcohol consumption or a large meal (see Color Image 54). Treatment includes allopurinol, probenecid, colchicine, and NSAIDs.

### Pseudogout



Calcium pyrophosphate crystals

Caused by deposition of calcium pyrophosphate crystals within the joint space. Forms basophilic, rhomboid crystals that are **weakly positively birefringent** (as opposed to the negatively birefringent, needle-shaped crystals in gout). Usually affects large joints (classically the knee). > 50 years old; both sexes affected equally. No treatment.

### Sarcoidosis

Characterized by immune-mediated, widespread noncaseating granulomas and elevated serum ACE levels. Common in black females.

Associated with restrictive lung disease, bilateral hilar lymphadenopathy, erythema nodosum, Bell's palsy, epithelial granulomas containing microscopic Schaumann and asteroid bodies, uveoparotitis, and hypercalcemia (due to elevated conversion of vitamin D to its active form in epithelioid macrophages) (see Image 104).

### GRAIN:

Gammaglobulinemia  
Rheumatoid arthritis  
ACE increase  
Interstitial fibrosis  
Noncaseating granulomas



**Seronegative  
spondylo-  
arthropathies**

Ankylosing  
spondylitis

Reiter's syndrome

Arthritis without rheumatoid factor (no anti-IgG antibody). Strong association with HLA-B27 (gene that codes for HLA MHC I). Occurs more often in males.

Chronic inflammatory disease of spine and sacroiliac joints → ankylosis (stiff spine), uveitis, and aortic regurgitation.

Classic triad:

1. Urethritis
2. Conjunctivitis and anterior uveitis
3. Arthritis

Bamboo spine.

“Can’t **see** (anterior uveitis/ conjunctivitis), can’t **pee** (urethritis), can’t climb a **tree** (arthritis).”

Post-GI or chlamydia infections.

**Scleroderma  
(progressive  
systemic  
sclerosis—PSS)**

Excessive fibrosis and collagen deposition throughout the body. 75% female. Commonly sclerosis of skin but also of cardiovascular and GI systems and kidney. 2 major categories:

1. Diffuse scleroderma—widespread skin involvement, rapid progression, early visceral involvement. Associated with anti-Scl-70 antibody.
2. **CREST** syndrome—**C**alcinosis, **R**aynaud’s phenomenon, **E**sophageal dysmotility, **S**clerodactyly, and **T**elangiectasia. Limited skin involvement, often confined to fingers and face. More benign clinical course. Associated with anticentromere antibody (see Color Image 53).

**Skin disorders**

Impetigo	Superficial skin infection. Honey crusting. Highly contagious.
Dermatitis	A group of inflammatory pruritic skin disorders. Etiology: allergy (usually type IV hypersensitivity), chemical injury, or infection.
Atopic dermatitis (eczema)	Pruritic eruption, commonly on flexor surfaces. Often associated with other atopic diseases (asthma, allergic rhinitis).
Allergic contact dermatitis	Type IV hypersensitivity reaction that follows exposure to allergen (poison ivy, poison oak, nickel, rubber, chemicals). Lesions occur at site of contact.
Psoriasis	Epidermal hyperplasia (acanthosis) with parakeratotic scaling (nuclei still in stratum corneum) especially on knees and elbows. ↑ stratum spinosum, ↓ <b>stratum granulosum</b> (see Color Image 65). Auspitz sign.
Dermatitis herpetiformis	Pruritic papules and vesicles. Deposits of IgA at the tips of dermal papillae. Associated with celiac disease.
Lichen planus	Pruritic, purple, polygonal papules; infiltrate of lymphocytes at dermoepidermal junction.
Erythema multiforme	Associated with infections, drugs, cancers, and autoimmune disease. Presents with multiple types of lesions, including macules, papules, vesicles, and <b>target lesions</b> (red papules with a pale central area). Stevens-Johnson syndrome (sulfa and anticonvulsant drugs) is the major form of erythema multiforme. Characterized by high fever, bulla formation and necrosis, ulceration of skin, and a high mortality rate.
Seborrheic keratosis	Flat, pigmented squamous epithelial proliferation with keratin-filled cysts ( <b>horn cysts</b> ). <b>Benign.</b>
Actinic keratosis	Caused by sun exposure. Small, rough erythematous or brownish papules. Premalignant lesion. Risk of carcinoma is proportional to epithelial dysplasia.
Keloid	Tumor of connective tissue elements of dermis that causes raised, thickened scars. Follows trauma to skin, especially in African-Americans.
Bullous pemphigoid	Autoimmune disorder with IgG antibody against epidermal basement membrane hemidesmosomes (linear immunofluorescence). Similar to but less severe than pemphigus vulgaris—affects skin but spares oral mucosa (see Color Image 64).
Pemphigus vulgaris	Potentially fatal autoimmune skin disorder. Intraepidermal bullae involving the oral mucosa and skin. Findings: acantholysis (breakdown of epithelial cell-to-cell junctions), IgG antibody against epidermal cell surface desmosomes (immunofluorescence throughout epidermis) (see Color Image 63).
Verrucae (warts)	Soft, tan-colored, cauliflowerlike lesions. Epidermal hyperplasia, hyperkeratosis, koilocytosis. Verruca vulgaris on hands, condyloma acuminatum on genitals.

**Skin cancer**

Squamous cell carcinoma	Very common. Associated with excessive exposure to sunlight and arsenic exposure. Commonly appear on hands and face. Locally invasive, but rarely metastasizes. Histopathology: keratin “pearls” (see Color Image 60).	<b>Actinic keratosis</b> is a precursor to squamous cell carcinoma.
Basal cell carcinoma	Most common in sun-exposed areas of body. Locally invasive, but almost never metastasizes. Gross pathology: pearly papules (see Color Image 62).	Basal cell tumors have “palisading” nuclei.
Melanoma	Common tumor with significant risk of metastasis. Associated with sunlight exposure; fair-skinned persons are at ↑ risk. Incidence ↑. <b>Depth</b> of tumor correlates with risk of metastasis (see Color Image 61).	Dysplastic nevus is a precursor to melanoma.

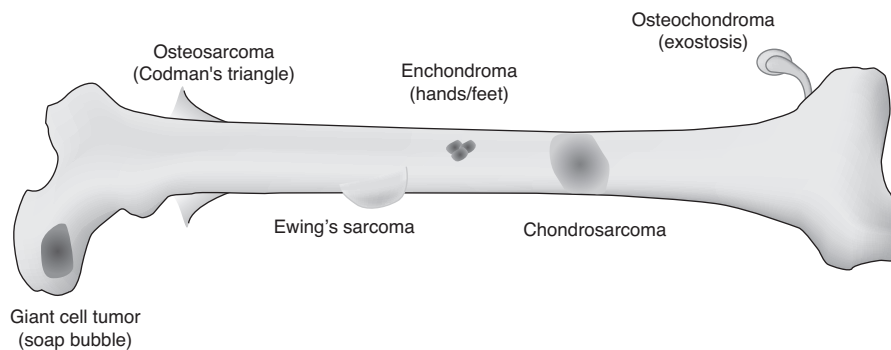
## Primary bone tumors

### Benign

Osteoid osteoma	Interlacing trabeculae of woven bone surrounded by osteoblasts. < 2 cm and found in proximal tibia and femur.
Osteoblastoma	Same morphologically as osteoid osteoma, but larger and found in vertebral column.
Giant cell tumor	Occurs most commonly at epiphyseal end of long bones. Peak incidence 20–40 years old. Locally aggressive benign tumor often around the distal femur, proximal tibial region. Characteristic “double bubble” or “soap bubble” appearance on x-ray. Spindle-shaped cells with multinucleated giant cells.
Osteochondroma (exostosis)	Most common benign bone tumor. Mature bone with cartilaginous cap. Usually in men < 25 years of age. Commonly originates from long metaphysis. Malignant transformation to chondrosarcoma is rare.
Enchondroma	Benign cartilaginous neoplasm found in intramedullary bone. Usually distal extremities (vs. chondrosarcoma).

### Malignant

Osteosarcoma (osteogenic carcinoma)	Most common 1° malignant tumor of bone. Peak incidence in men 10–20 years old. Commonly found in the metaphysis of long bones. Predisposing factors include Paget’s disease of bone, bone infarcts, radiation, and familial retinoblastoma. Codman’s triangle (from elevation of periosteum) on x-ray.
Ewing’s sarcoma	Anaplastic small blue cell malignant tumor. Most common in boys < 15. Extremely aggressive with early mets, but responsive to chemotherapy. Characteristic “onion-skin” appearance in bone (“going out for Ewings and onion rings.”) Commonly appears in diaphysis of long bones, pelvis, scapula, and ribs. 11;22 translocation.
Chondrosarcoma	Malignant cartilaginous tumor. Most common in men aged 30–60. Usually located in pelvis, spine, scapula, humerus, tibia, or femur. May be of 1° origin or from osteochondroma. Expansile glistening mass within the medullary cavity.



## Buerger’s disease

Findings	Also known as thromboangiitis obliterans; idiopathic, segmental, thrombosing vasculitis of intermediate and small peripheral arteries and veins. Seen in heavy smokers. Intermittent claudication, superficial nodular phlebitis, cold sensitivity (Raynaud’s phenomenon), severe pain in affected part; may lead to gangrene.
Treatment	Quit smoking.

<b>Takayasu's arteritis</b>	Known as “pulseless disease”—granulomatous thickening of aortic arch and/or proximal great vessels. Associated with an elevated ESR. Primarily affects Asian females < 40 years old. <b>F</b> ever, <b>A</b> rthritis, <b>N</b> ight sweats, <b>M</b> Yalgia, <b>S</b> KIN nodules, <b>O</b> cular disturbances, <b>W</b> eak pulses in upper extremities.	Affects medium and large arteries.  <b>FAN MY SKIN On</b> Wednesday.
<b>Temporal arteritis (giant cell arteritis)</b>	Most common vasculitis that affects medium and small arteries, usually branches of carotid artery. Focal, granulomatous. Findings include unilateral headache, jaw claudication, impaired vision (occlusion of ophthalmic artery, which can lead to blindness). Half of patients have systemic involvement and polymyalgia rheumatica (proximal muscle pain, periarticular pain). Associated with elevated ESR. Responds well to steroids.	<b>TEM</b> poral = signs near <b>TEM</b> ples. ESR is markedly elevated. Affects elderly females.
<b>Polyarteritis nodosa</b>	Characterized by necrotizing immune complex inflammation of medium-sized muscular arteries, typically involving renal and visceral vessels.	Lesions are of different ages.
Symptoms	Fever, weight loss, malaise, abdominal pain, melena, headache, myalgia, hypertension, neurologic dysfunction, cutaneous eruptions.	
Findings	Hepatitis B seropositivity in 30% of patients. Multiple aneurysms and constrictions on arteriogram. Typically not associated with ANCA.	
Treatment	Corticosteroids, cyclophosphamide.	
<b>Wegener's granulomatosis</b>	Characterized by triad of focal necrotizing vasculitis, necrotizing granulomas in the lung and upper airway, and necrotizing glomerulonephritis.	
Symptoms	Perforation of nasal septum, chronic sinusitis, otitis media, mastoiditis, cough, dyspnea, hemoptysis, hematuria.	
Findings	C-ANCA is a strong marker of disease; chest x-ray may reveal large nodular densities; hematuria and red cell casts.	
Treatment	Cyclophosphamide and corticosteroids.	
<b>Other ANCA-positive vasculitides</b>		
Microscopic polyangiitis	Like Wegener's but lacks granulomas. P-ANCA.	
1° pauci-immune crescentic glomerulonephritis	Vasculitis limited to kidney.	
Churg-Strauss syndrome	Granulomatous vasculitis with eosinophilia. Involves lung, heart, skin, kidneys, nerves. Often seen in atopic patients.	

► **MUSCULOSKELETAL AND CONNECTIVE TISSUE—PATHOLOGY** (*continued*)

<b>Kawasaki disease</b>	Acute, self-limiting disease of infants/kids. Acute necrotizing vasculitis of small/medium-sized vessels. Fever, congested conjunctiva, changes in lips/oral mucosa, lymphadenitis. May develop coronary aneurysms.
<b>Henoch-Schönlein purpura</b>	Most common form of childhood systemic vasculitis. Skin rash (palpable purpura), arthralgia, intestinal hemorrhage, abdominal pain, and melena. Multiple lesions of the same age.
<b>Telangiectasia</b>	Arteriovenous malformation in small vessels. Looks like dilated capillary. Hereditary hemorrhagic telangiectasia—autosomal dominant inheritance. Presents with nosebleeds and skin discolorations.

► **MUSCULOSKELETAL AND CONNECTIVE TISSUE—PHARMACOLOGY**

<b>Opioid analgesics</b>	Morphine, fentanyl, codeine, heroin, methadone, meperidine, dextromethorphan.
Mechanism	Act as agonists at opioid receptors ( $\mu$ = morphine, $\delta$ = enkephalin, $\kappa$ = dynorphin) to modulate synaptic transmission.
Clinical use	Pain, cough suppression (dextromethorphan), diarrhea (loperamide and diphenoxylate), acute pulmonary edema, maintenance programs for addicts (methadone).
Toxicity	Addiction, <b>respiratory depression</b> , constipation, miosis ( <b>pinpoint pupils</b> ), additive <b>CNS depression</b> with other drugs. Tolerance does not develop to miosis and constipation. Toxicity treated with naloxone or naltrexone (opioid receptor antagonist). $O_2$ is contraindicated if morphine overdose—might contribute to respiratory failure.

**Arachidonic acid products**

Lipoxygenase pathway yields Leukotrienes.

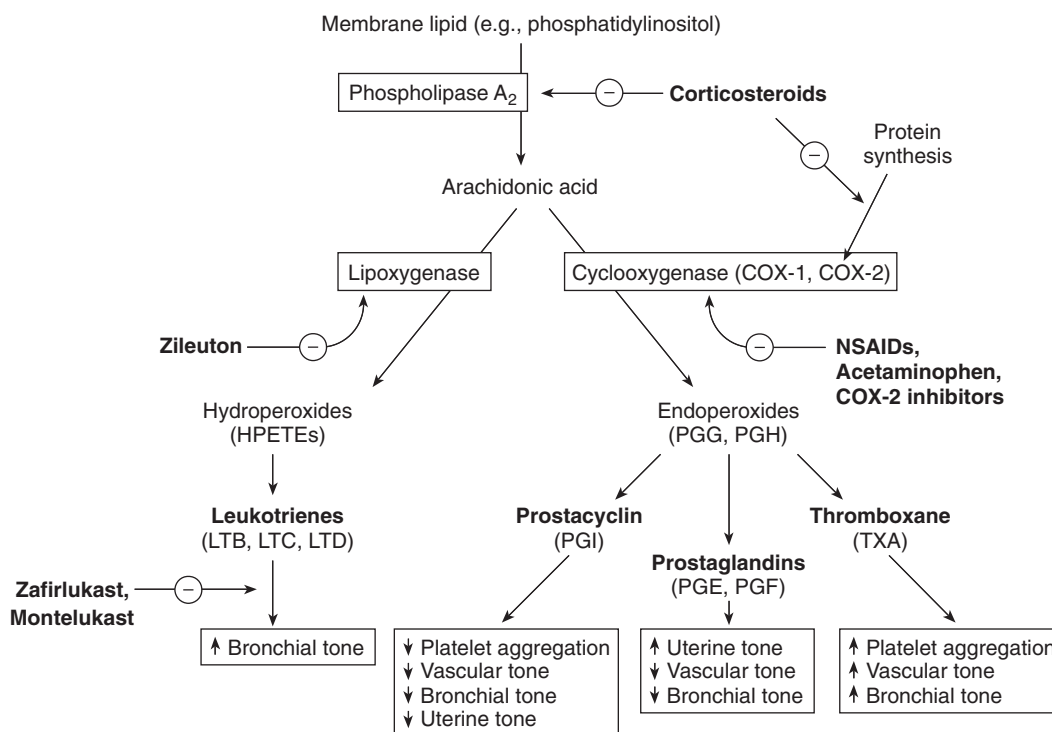
LTB<sub>4</sub> is a neutrophil chemotactic agent.

LTC<sub>4</sub>, D<sub>4</sub>, and E<sub>4</sub> function in bronchoconstriction, vasoconstriction, contraction of smooth muscle, and ↑ vascular permeability.

PGI<sub>2</sub> inhibits platelet aggregation and promotes vasodilation.

L for Lipoxygenase and Leukotriene.

Platelet-Gathering Inhibitor.



(Adapted, with permission, from Katzung BG, Trevor AJ. *Pharmacology: Examination & Board Review*, 5th ed. Stamford, CT: Appleton & Lange, 1998:150.)

**NSAIDs**

Mechanism

Ibuprofen, naproxen, indomethacin, ketorolac.

Clinical use

Reversibly inhibit cyclooxygenase (both COX-1 and COX-2). Block prostaglandin synthesis.

Toxicity

Antipyretic, analgesic, anti-inflammatory. Indomethacin is used to close a PDA. Renal damage, aplastic anemia, GI distress, ulcers.

**COX-2 inhibitors (celecoxib, valdecoxib)**

Mechanism

Reversibly inhibit specifically the cyclooxygenase (COX) isoform 2, which is found in inflammatory cells and mediates inflammation and pain; spares COX-1, which helps maintain the gastric mucosa. Thus, should not have the corrosive effects of other NSAIDs on the GI lining.

Clinical use

Rheumatoid and osteoarthritis.

Toxicity

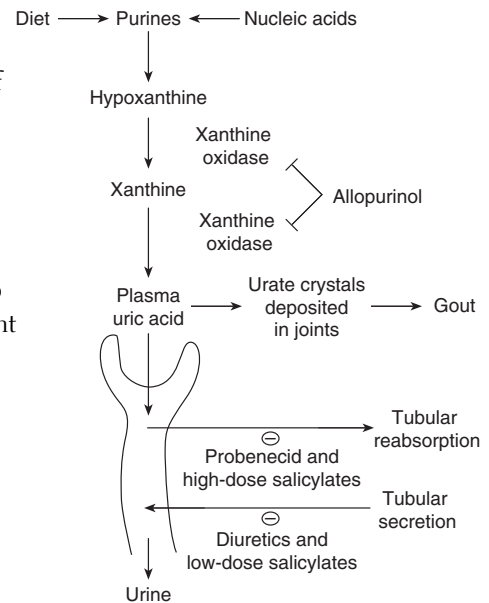
Increased risk of thrombosis. Less toxicity to GI mucosa (lower incidence of ulcers, bleeding).

### Acetaminophen

Mechanism	Reversibly inhibits cyclooxygenase, mostly in CNS. Inactivated peripherally.
Clinical use	Antipyretic, analgesic, but lacking anti-inflammatory properties.
Toxicity	Overdose produces hepatic necrosis; acetaminophen metabolite depletes glutathione and forms toxic tissue adducts in liver. N-acetylcysteine is antidote—regenerates glutathione.

### Gout drugs

Colchicine	Acute gout. Depolymerizes microtubules, impairing leukocyte chemotaxis and degranulation. GI side effects, especially if given orally. (Note: indomethacin is less toxic, more commonly used.)
Probenecid	Chronic gout. Inhibits reabsorption of uric acid (also inhibits secretion of penicillin).
Allopurinol	Chronic gout. Inhibits xanthine oxidase, ↓ conversion of xanthine to uric acid. Also used in lymphoma and leukemia to prevent tumor lysis–associated urate nephropathy.



### Etanercept

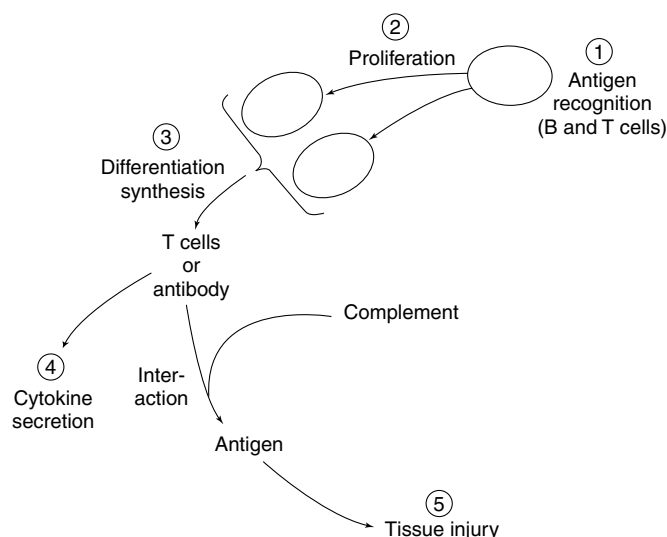
Mechanism	Recombinant form of human TNF receptor that binds TNF- $\alpha$ .
Clinical use	Rheumatoid arthritis, psoriasis, ankylosing spondylitis.

### Infliximab

Mechanism	TNF- $\alpha$ antibody.
Clinical use	Crohn's disease, rheumatoid arthritis, ankylosing spondylitis.
Toxicity	Predisposes to infections (reactivation of latent TB).

**Immunosuppressive agents: sites of action**

Agent	Site
Prednisone	2, 5
Cyclosporine	2, 3
Azathioprine	2
Methotrexate	2
Dactinomycin	2, 3
Cyclophosphamide	2
Antilymphocytic globulin and monoclonal anti-T-cell antibodies	1, 2, 3
Rh <sub>3</sub> (D) immune globulin	1
Tacrolimus	4



(Adapted, with permission, from Katzung BG. *Basic and Clinical Pharmacology*, 7th ed. Stamford, CT: Appleton & Lange, 1997:924.)

**Cyclosporine**

Mechanism	Binds to cyclophilins. Complex blocks the differentiation and activation of T cells by inhibiting calcineurin, thus preventing the production of IL-2 and its receptor.
Clinical use	Suppresses organ rejection after transplantation; selected autoimmune disorders.
Toxicity	Predisposes patients to viral infections and lymphoma; nephrotoxic (preventable with mannitol diuresis).

**Tacrolimus (FK506)**

Mechanism	Similar to cyclosporine; binds to FK-binding protein, inhibiting secretion of IL-2 and other cytokines.
Clinical use	Potent immunosuppressive used in organ transplant recipients.
Toxicity	Significant—nephrotoxicity, peripheral neuropathy, hypertension, pleural effusion, hyperglycemia.

**Azathioprine**

Mechanism	Antimetabolite derivative of 6-mercaptopurine that interferes with the metabolism and synthesis of nucleic acids. Toxic to proliferating lymphocytes.
Clinical use	Kidney transplantation, autoimmune disorders (including glomerulonephritis and hemolytic anemia).
Toxicity	Bone marrow suppression. Active metabolite mercaptopurine is metabolized by xanthine oxidase; thus, toxic effects may be ↑ by allopurinol.



**Recombinant cytokines and clinical uses**

Agent	Clinical uses
Aldesleukin (interleukin-2)	Renal cell carcinoma, metastatic melanoma
Erythropoietin (epoetin)	Anemias (especially in renal failure)
Filgrastim (granulocyte colony-stimulating factor)	Recovery of bone marrow
Sargramostim (granulocyte-macrophage colony-stimulating factor)	Recovery of bone marrow
$\alpha$ -interferon	Hepatitis B and C, Kaposi's sarcoma, leukemias, malignant melanoma
$\beta$ -interferon	Multiple sclerosis
$\gamma$ -interferon	Chronic granulomatous disease
Oprelvekin (interleukin-11)	Thrombocytopenia
Thrombopoietin	Thrombocytopenia

# Neurology

*“Estimated amount of glucose used by an adult human brain each day, expressed in M&Ms: 250.”*

—Harper's Index

*“He has two neurons held together by a spirochete.”*

—Anonymous

- ▶ High-Yield Clinical Vignettes
- ▶ Anatomy and Physiology
- ▶ Pathology
- ▶ Pharmacology

- Patient presents with ↓ pain and temperature sensation over the lateral aspects of both arms.
- Penlight in patient's right eye produces bilateral pupillary constriction. When moved to the left eye, there is paradoxical dilatation.
- Patient describes ↓ prick sensation on the lateral aspect of her leg and foot.
- Elderly woman presents with arthritis and tingling over the lateral digits of her right hand.
- 20-year-old dancer reports ↓ plantar flexion and ↓ sensation over the back of her thigh, calf, and lateral half of her foot.
- Woman involved in a motor vehicle accident cannot turn her head to the left and has right shoulder droop.
- Man presents with one wild, flailing arm.
- Patient with cortical lesion does not know that he has a disease.
- Patient cannot protrude tongue toward left side and has a right-sided spastic paralysis.
- Teen falls while rollerblading and hurts his elbow. He can't feel the medial part of his palm.
- Field hockey player presents to the ER after falling on her arm during practice. X-ray shows midshaft break of the humerus.
- Patient cannot blink his right eye or seal his lips and has mild ptosis on the right side.
- Patient complains of pain, numbness, and a tingling sensation. On exam, she has wasting of the thenar eminence.

What is the lesion?

Syringomyelia.

What is the defect?

Atrophy of the left optic nerve.

A deficit in what muscular action can also be expected?

Dorsiflexion and eversion of foot (common peroneal nerve).

What is the diagnosis?

Carpal tunnel syndrome, median nerve compression.

What spinal nerve is involved?

Tibial (L4–S3).

What structure is damaged?

Right CN XI (runs through jugular foramen with CN IX and X), innervating sternocleidomastoid and trapezius muscles.

Where is the lesion?

Contralateral subthalamic nucleus (hemiballismus).

Where is the lesion?

Right parietal lobe.

Where is the lesion?

Left medulla, CN XII.

Which nerve and what injury?

Ulnar nerve due to broken medial condyle.

Which nerve and which artery are most likely damaged?

Radial nerve and deep brachial artery, which run together.

What is the diagnosis, and which nerve is affected?

Bell's palsy; CN VII.

What is the diagnosis, and what nerve is often affected?

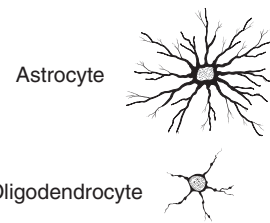
Carpal tunnel syndrome; median nerve.

► **NEUROLOGY—HIGH-YIELD CLINICAL VIGNETTES** (*continued*)

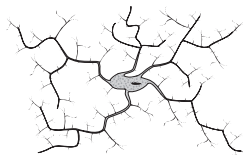
- |                                                                                                                                                                              |                        |                     |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|---------------------|
| ■ Woman presents with headache, visual disturbance, galactorrhea, and amenorrhea.                                                                                            | What is the diagnosis? | Prolactinoma.       |
| ■ 43-year-old man experiences dizziness and tinnitus. CT shows enlarged internal acoustic meatus.                                                                            | What is the diagnosis? | Schwannoma.         |
| ■ 25-year-old female presents with sudden uniocular vision loss and slightly slurred speech. She has a history of weakness and paresthesias that have resolved.              | What is the diagnosis? | Multiple sclerosis. |
| ■ 10-year-old child “spaces out” in class (e.g., stops talking midsentence and then continues as if nothing had happened). During spells, there is slight quivering of lips. | What is the diagnosis? | Absence seizures.   |

**CNS/PNS  
supportive cells**

Astrocytes—physical support, repair,  $K^+$  metabolism; help maintain blood-brain barrier. Astrocyte marker: GFAP.  
Ependymal cells—inner lining of ventricles.  
Microglia—phagocytosis.  
Oligodendroglia—central myelin production.  
Schwann cells—peripheral myelin production.  
Microglia, like macrophages, originate from mesoderm. All other CNS/PNS supportive cells originate from ectoderm.



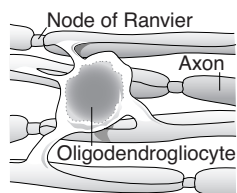
**Microglia**



CNS phagocytes. Mesodermal origin. Not readily discernible in Nissl stains. Have small irregular nuclei and relatively little cytoplasm. In response to tissue damage, transform into large ameboid phagocytic cells.

HIV-infected microglia fuse to form multinucleated giant cells in the CNS.

**Oligodendroglia**



Each oligodendrocyte myelinates multiple CNS axons, up to 30 each. In Nissl stains, they appear as small nuclei with dark chromatin and little cytoplasm. Predominant type of glial cell in white matter.

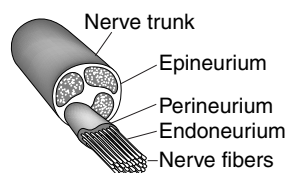
These cells are destroyed in multiple sclerosis.

**Schwann cells**

Each Schwann cell myelinates only 1 PNS axon. Also promote axonal regeneration.

Acoustic neuroma is an example of a schwannoma. Location commonly associated with internal acoustic meatus (CN VII, VIII).

**Peripheral nerve  
layers**



Endoneurium invests single nerve fiber.  
Perineurium (permeability barrier) surrounds a fascicle of nerve fibers.  
Epineurium (dense connective tissue) surrounds entire nerve (fascicles and blood vessels).

Perineurium—Permeability barrier; must be rejoined in microsurgery for limb reattachment.  
*Endo* = inner.  
*Peri* = around.  
*Epi* = outer.

## Sensory corpuscles

### Meissner's

Small, encapsulated nerve endings found in dermis of palms, soles, and digits of skin. Involved in light discriminatory touch of glabrous (hairless) skin.



### Pacinian

Large, encapsulated nerve endings found in deeper layers of skin at ligaments, joint capsules, serous membranes, mesenteries. Involved in pressure, coarse touch, vibration, and tension.

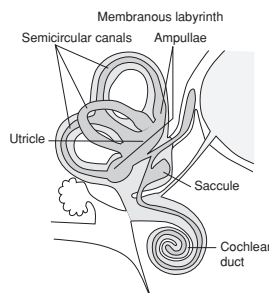


### Merkel's

Cup-shaped nerve endings (tactile disks) in dermis of fingertips, hair follicles, hard palate. Involved in light, crude touch.



## Inner ear



Consists of a series of tubes in the temporal bone (bony labyrinth) filled with perilymph ( $\text{Na}^+$  rich, similar to ECF) that includes cochlea, vestibule, and semicircular canals. Within the bony labyrinth is a 2nd series of tubes (membranous labyrinth) filled with endolymph ( $\text{K}^+$  rich, similar to ICF) that includes cochlear duct (within the cochlea), utricle and saccule (within the vestibule), and semicircular canals. Hair cells are the sensory elements in both vestibular apparatus (spatial orientation) and cochlea (hearing).

Base of the cochlea (narrow and stiff) picks up high-frequency sound. Apex of the cochlea (wide and flexible) picks up low-frequency sound.

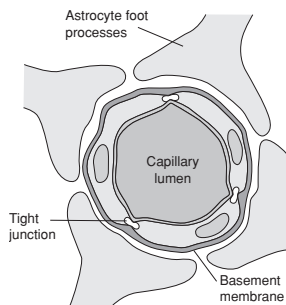
*Peri*—think outside of cell ( $\text{Na}^+$ ).  
*Endo*—think inside of cell ( $\text{K}^+$ ).  
Endolymph is made by the stria vascularis.

Utricle and saccule contain maculae—detect linear acceleration.

Semicircular canals contain Ampullae—detect Angular acceleration.

Hearing loss in the elderly—high frequency  $\rightarrow$  low frequency.

## Blood-brain barrier



Formed by 3 structures:

1. Tight junctions between nonfenestrated capillary endothelial cells
2. Astrocyte processes
3. Basement membrane

Glucose and amino acids cross by carrier-mediated transport mechanism.

Nonpolar/lipid-soluble substances cross more readily than do polar/water-soluble ones.

A few specialized brain regions with fenestrated capillaries and no blood-brain barrier allow molecules in the blood to affect brain function (e.g., area postrema—vomiting after chemo) or neurosecretory products to enter circulation (e.g., neurohypophysis—ADH release).

Other barriers include:

1. Blood-testis barrier
2. Maternal-fetal blood barrier of placenta

Infarction destroys endothelial cell tight junctions  $\rightarrow$  vasogenic edema.

**Hypothalamus functions**

Thirst and water balance (supraoptic nucleus).  
 Adenohypophysis control via releasing factors.  
 Neurohypophysis and median eminence release hormones synthesized in hypothalamic nuclei.  
**Hunger** (lateral nucleus—destruction → anorexia and starvation) and satiety (ventromedial nucleus—destruction → hyperphagia and obesity).  
 Autonomic regulation (anterior hypothalamus regulates parasympathetic; posterior hypothalamus regulates sympathetic), circadian rhythms (suprachiasmatic nucleus).  
 Temperature regulation (posterior hypothalamus regulates heat conservation and production when cold; Anterior hypothalamus coordinates Cooling when hot).  
 Sexual urges and emotions (Septal nucleus—destruction → rage).

The hypothalamus wears **TAN HATS**.

If you zap your **ventromedial** nucleus, you grow **ventrally** and **medially**.

If you zap your **Posterior** hypothalamus, you become a **Poikilotherm** (cold-blooded snake).

**A/C** = anterior cooling.

**Posterior pituitary (neurohypophysis)**

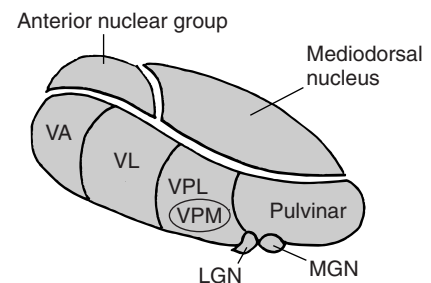
Receives hypothalamic axonal projections from supraoptic (ADH) and paraventricular (oxytocin) nuclei.

Oxytocin: *oxys* = quick; *tocos* = birth.

**Thalamus**

Major relay for ascending sensory information that ultimately reaches the cortex.  
**Lateral geniculate nucleus (LGN)**—visual.  
**Medial geniculate nucleus (MGN)**—auditory.  
**Ventral posterior nucleus, lateral part (VPL)**—body sensation (proprioception, pressure, pain, touch, vibration via dorsal columns, spinothalamic tract).  
**Ventral posterior nucleus, medial part (VPM)**—facial sensation (via CN V).  
**Ventral anterior/lateral (VA/VL) nuclei**—motor.

**Lateral for Light.**  
**Medial for Music.**



## Limbic system

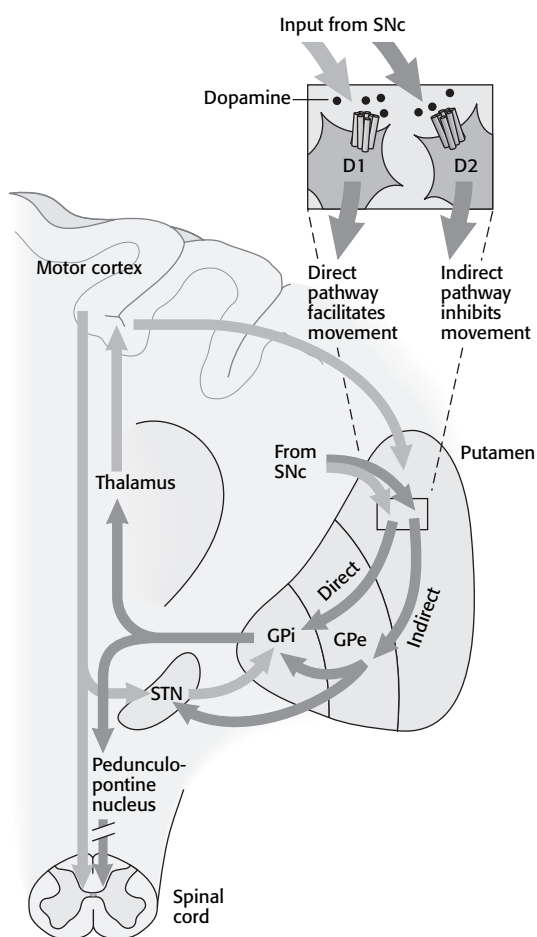
Responsible for Feeding, Fighting, Feeling, Flight, and sex.

The famous 5 F's.

## Basal ganglia

Important in voluntary movements and making postural adjustments.

Parkinson's disease symptoms due to ↓ input from the substantia nigra (leading to ↓ stimulation of the direct pathway and ↓ inhibition of the indirect pathway).



■ stimulatory

■ inhibitory

SNc Substantia nigra pars compacta

GPe Globus pallidus externus

GPi Globus pallidus internus

STN Subthalamic nucleus

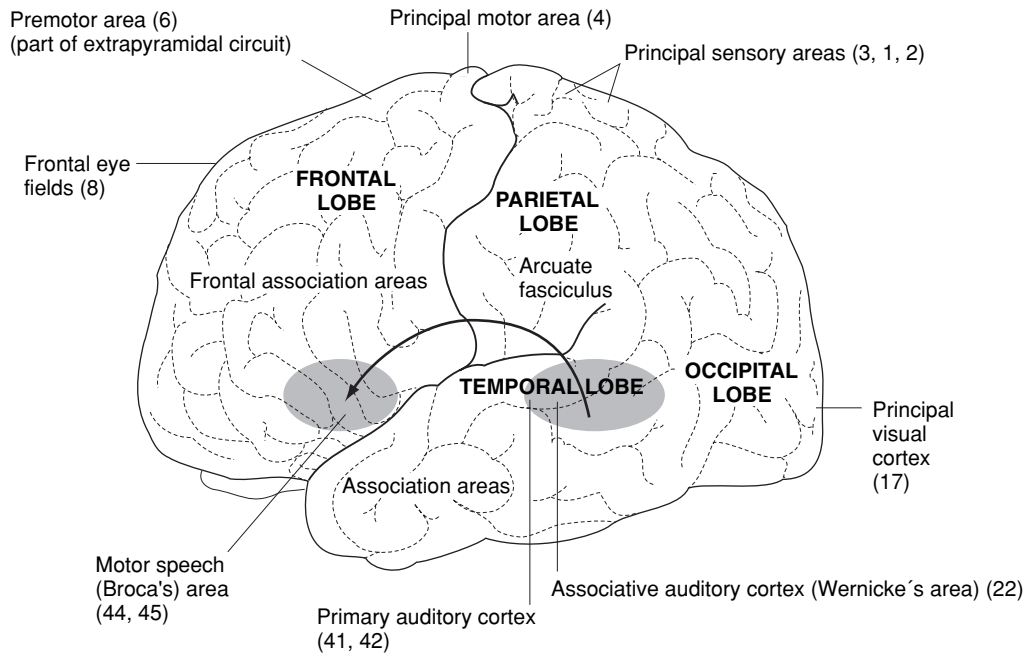
D1 Dopamine D1 receptor

D2 Dopamine D2 receptor

(Adapted, with permission, from Kandel ER, Schwartz JH, Jessell TM. *Principles of Neural Science*, 4th ed. Stamford, CT: Appleton & Lange, 2000:860.)



### Cerebral cortex functions

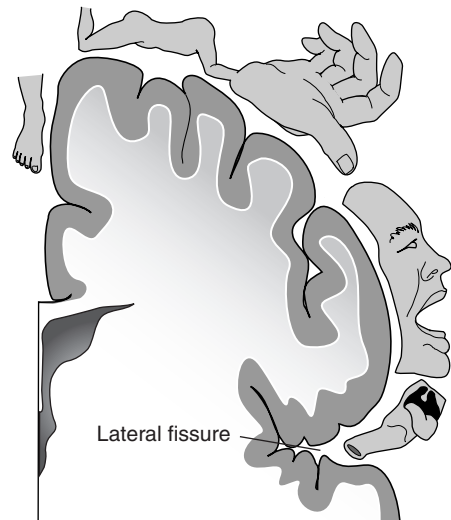


#### Frontal lobe functions

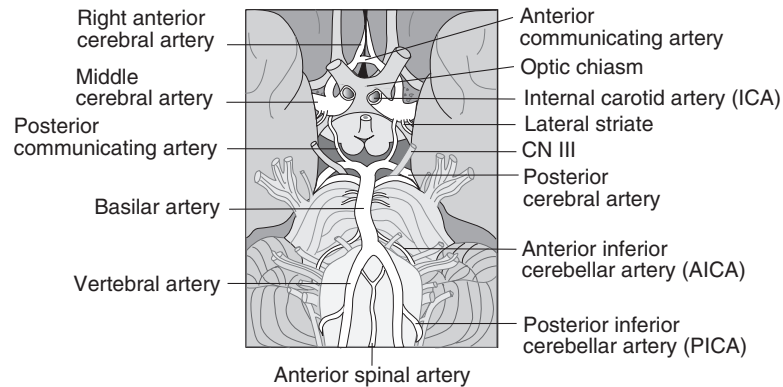
“Executive functions”—planning, inhibition, concentration, orientation, language, abstraction, judgment, motor regulation, mood. Lack of social judgment is most notable in frontal lobe lesion.

#### Homunculus

Topographical representation of sensory and motor areas in the cerebral cortex. Use to localize lesion (e.g., in blood supply) leading to specific defects. For example, lower extremity deficit in sensation or movement indicates involvement of the anterior cerebral artery (see following entry).



## Circle of Willis



Anterior cerebral artery—supplies medial surface of the brain, leg-foot area of motor and sensory cortices.

Middle cerebral artery—supplies lateral aspect of brain, trunk-arm-face area of motor and sensory cortices, Broca's and Wernicke's speech areas.

Anterior communicating artery—most common site of circle of Willis aneurysm; lesions may cause visual-field defects.

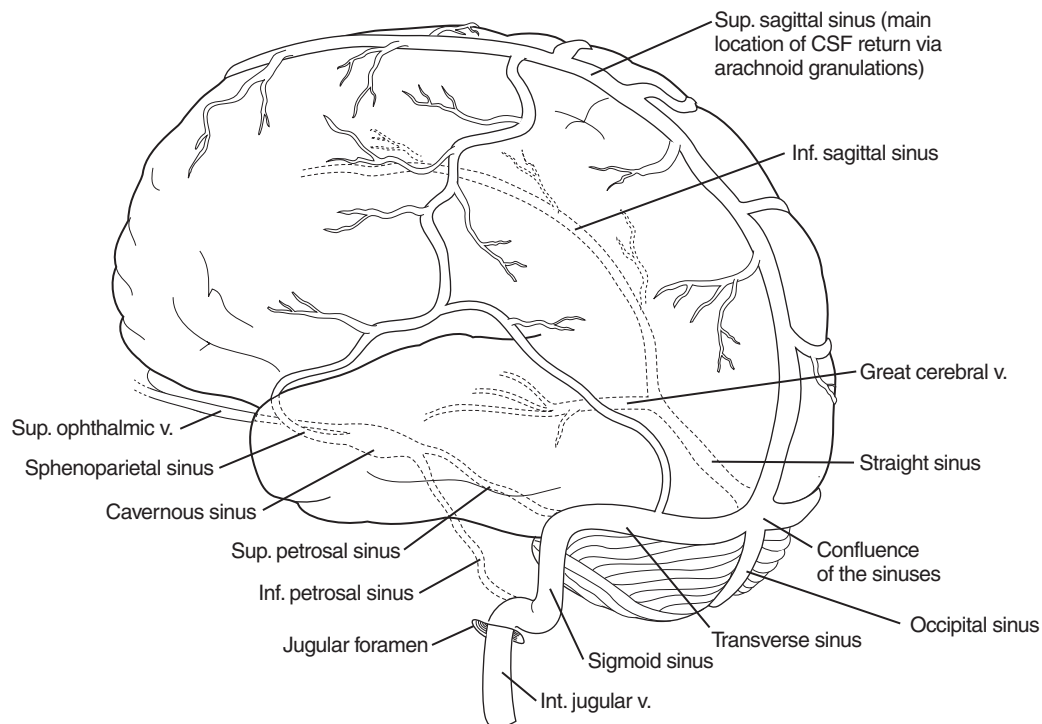
Posterior communicating artery—common area of aneurysm; causes CN III palsy.

Lateral striate—divisions of middle cerebral artery; “arteries of stroke”; supply internal capsule, caudate, putamen, globus pallidus.

In general, stroke of anterior circle → general sensory and motor dysfunction, aphasia; stroke of posterior circle → cranial nerve deficits (vertigo, visual deficits), coma, cerebellar deficits (ataxia).

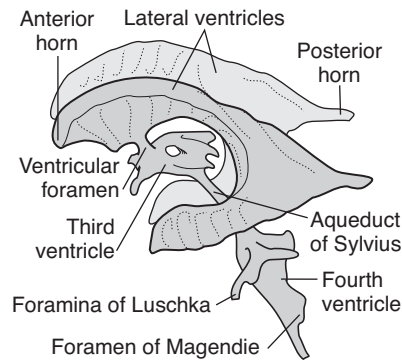
## Dural venous sinuses

Venous sinuses run in the dura mater where its meningeal and periosteal layers separate. Cerebral veins → venous sinuses → internal jugular vein.



(Adapted, with permission, from White JS. *USMLE Road Map: Gross Anatomy*, 1st ed. New York: McGraw-Hill, 2003.)

## Ventricular system



Lateral ventricle → 3rd ventricle via foramen of Monro.

3rd ventricle → 4th ventricle via aqueduct of Sylvius.

4th ventricle → subarachnoid space via:

Foramina of Luschka = lateral.

Foramen of Magendie = medial.

## Spinal nerves

There are 31 spinal nerves altogether: 8 cervical, 12 thoracic, 5 lumbar, 5 sacral, 1 coccygeal.

31, just like 31 flavors!

Vertebral disk herniation usually occurs between L5 and S1.

## Spinal cord lower extent

In adults, spinal cord extends to lower border of L1–L2; subarachnoid space extends to lower border of S2. Lumbar puncture is usually performed in L3–L4 or L4–L5 interspaces, at level of cauda equina.

To keep the cord **alive**, keep the spinal needle between **L3 and L5**.

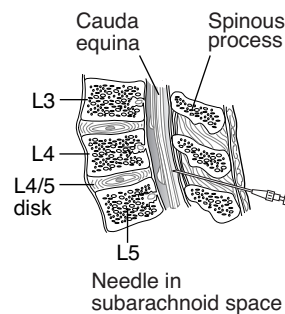
## Lumbar puncture

CSF obtained from lumbar subarachnoid space between L4 and L5 (at the level of iliac crests).

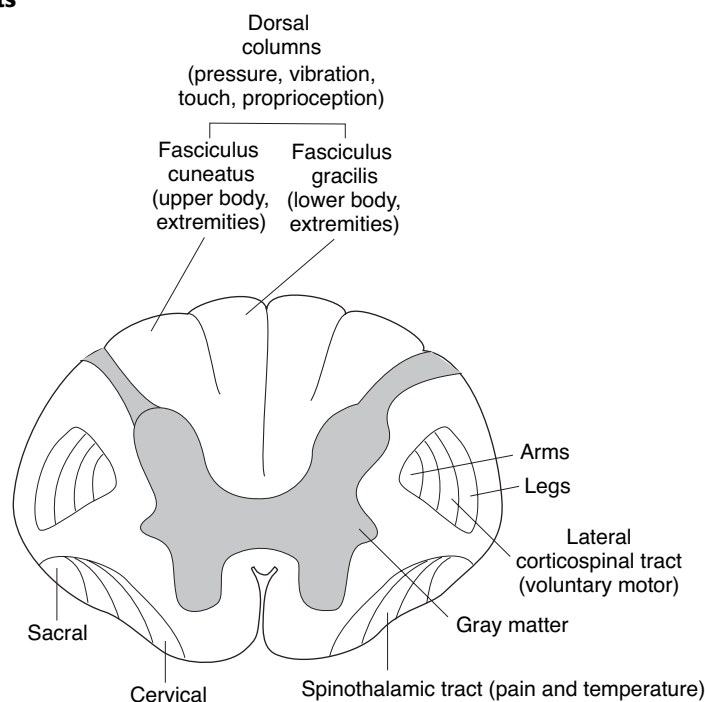
Structures pierced as follows:

1. Skin/superficial fascia
2. Ligaments (supraspinous, interspinous, ligamentum flavum)
3. Epidural space
4. Dura mater
5. Subdural space
6. Arachnoid
7. Subarachnoid space—CSF

**Pia** is not pierced.



## Spinal cord and associated tracts



## Spinal tract anatomy and functions

Tract and function	1st-order neuron	Synapse 1	2nd-order neuron	Synapse 2	3rd-order neuron
Dorsal column-medial lemniscal pathway (ascending pressure, vibration, touch, and proprioceptive sensation)	Sensory nerve ending → dorsal root ganglion → enters spinal cord, ascends ipsilaterally in dorsal column	Nucleus cuneatus or gracilis (medulla)	Decussates in medulla → ascends contralaterally in medial lemniscus	VPL of thalamus	Sensory cortex
Spinothalamic tract (ascending pain and temperature sensation)	Sensory nerve ending (A-delta and C fibers) → enters spinal cord	Ipsilateral gray matter (spinal cord)	Decussates at anterior white commissure → ascends contralaterally	VPL of thalamus	Sensory cortex
Lateral corticospinal tract (descending voluntary movement of contralateral limbs)	<b>Upper motor neuron:</b> 1° motor cortex → descends ipsilaterally until decussating at caudal medulla (pyramidal decussation) → descends contralaterally	Cell body of anterior horn (spinal cord)	<b>Lower motor neuron:</b> Leaves spinal cord	Neuromuscular junction	

## Dorsal column organization

Fasciculus gracilis = legs.  
Fasciculus cuneatus = arms.

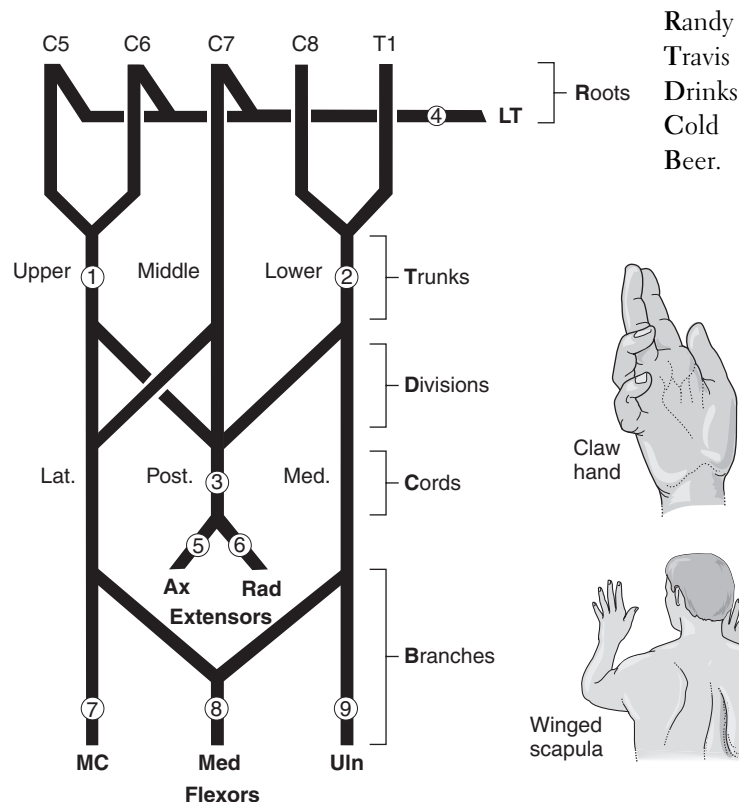
Dorsal column is organized as you are, with hands at sides—arms outside and legs inside.

## Brachial plexus

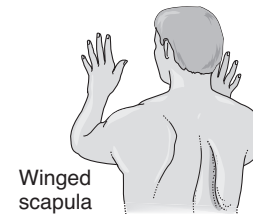
1. Waiter's tip (Erb's palsy)
2. Claw hand (Klumpke's palsy)
3. Wrist drop
4. Winged scapula
5. Deltoid paralysis
6. Saturday night palsy (wrist drop)
7. Difficulty flexing elbow, variable sensory loss
8. Decreased thumb function, Pope's blessing
9. Intrinsic muscles of hand, claw hand

**Rad** = radial nerve  
**Ax** = axillary nerve  
**LT** = long thoracic nerve  
**MC** = musculocutaneous nerve  
**Med** = median nerve  
**Uln** = ulnar nerve

Clavicle fracture is relatively common—brachial plexus is protected from injury by subclavius muscle.

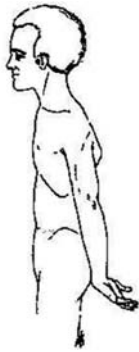


Randy  
Travis  
Drinks  
Cold  
Beer.



## Upper extremity nerve injury

Nerve	Site of injury/deficit in motion	Deficit in sensation/course
Radial	Shaft of humerus—loss of triceps brachii (triceps reflex), brachioradialis (brachioradialis reflex), and extensor carpi radialis longus (→ wrist drop).	Posterior brachial cutaneous. Posterior antebrachial cutaneous. Passes through supinator.
Median	Supracondyle of humerus—no loss of power in any of the arm muscles; loss of forearm pronation, wrist flexion, finger flexion, and several thumb movements; eventually, thenar atrophy.	Loss of sensation over the lateral palm and thumb and the radial 2½ fingers. Passes through pronator teres.
Ulnar	Medial epicondyle—impaired wrist flexion and adduction, and impaired adduction of thumb and the ulnar 2 fingers (→ claw hand).	Loss of sensation over the medial palm and ulnar 1½ fingers. Passes through flexor carpi ulnaris.
Axillary	Surgical neck of humerus or anterior shoulder dislocation—loss of deltoid action.	
Musculocutaneous	Loss of function of coracobrachialis, biceps, and brachialis muscles (biceps reflex).	Passes through coracobrachialis.

**Erb-Duchenne palsy**

Traction or tear of the upper trunk of the brachial plexus (C5 and C6 roots); follows blow to shoulder or trauma during delivery.

Findings: limb hangs by side (paralysis of abductors), medially rotated (paralysis of lateral rotators), forearm is pronated (loss of biceps).

“Waiter’s tip” owing to appearance of arm.

**Thoracic outlet syndrome (Klumpke’s palsy)**

An embryologic defect; can compress subclavian artery and inferior trunk of brachial plexus (C8, T1), resulting in thoracic outlet syndrome:

1. Atrophy of the thenar and hypothenar eminences
2. Atrophy of the interosseous muscles
3. Sensory deficits on the medial side of the forearm and hand
4. Disappearance of the radial pulse upon moving the head toward the opposite side

**Lower extremity nerve injury****Nerve**

Common peroneal (L4–S2)

**Deficit in motion**

Loss of dorsiflexion (→ foot drop). Deep peroneal nerve innervates anterior compartment; superficial peroneal nerve innervates lateral compartment.

**PED** = Peroneal Everts and Dorsiflexes; if injured, foot drop**PED**.

Tibial (L4–S3)

Loss of plantar flexion. Tibial nerve innervates posterior compartment.

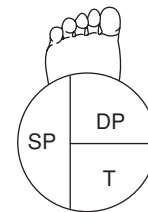
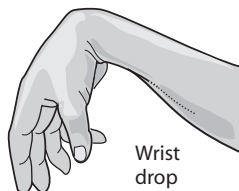
**TIP** = Tibial Inverts and Plantarflexes; if injured, can’t stand on **TIP**toes.

Femoral (L2–L4)

Loss of knee extension/knee jerk.

Obturator (L2–L4)

Loss of hip adduction.

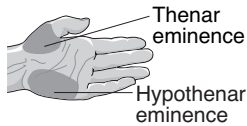
**Radial nerve**

Known as the “great extensor nerve.” Provides innervation of the **B**rachioradialis, **E**xtensors of the wrist and fingers, **S**upinator, and **T**riceps.

Radial nerve innervates the **BEST**!

To **SUP**inate is to move as if carrying a bowl of **SOUP**.

**Thenar-hypothenar muscles**



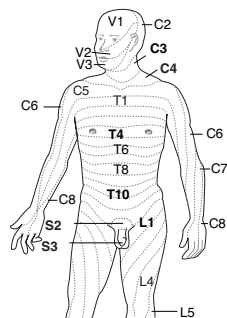
Thenar—Opponens pollicis, Abductor pollicis brevis, Flexor pollicis brevis.  
Hypothenar—Opponens digiti minimi, Abductor digiti minimi, Flexor digiti minimi.

Both groups perform the same functions: **O**ppose, **A**bduct, and **F**lex (**OAF**).

**Clinically important landmarks**

Pudendal nerve block—ischial spine.  
Appendix— $\frac{2}{3}$  of the way from the umbilicus to the anterior superior iliac spine (McBurney's point).  
Lumbar puncture—iliac crest.

**Landmark dermatomes**



C2 is the posterior half of a skull “cap.”  
C3 is a high turtleneck shirt.  
C4 is a low-collar shirt.  
T4 is at the nipple.  
T7 is at the thyroid process.  
T10 is at the umbilicus (important for early appendicitis pain referral).  
L1 is at the inguinal ligament.  
L4 includes the kneecaps.  
S2, S3, S4 erection and sensation of penile and anal zones.

Gallbladder pain referred to the right shoulder via the phrenic nerve.  
**T4** at the **teat** pore.  
**T10** at the belly but **TEN**.  
L1 is **IL** (Inguinal Ligament).  
Down on **L4s** (**all** **four**s).  
“**S2, 3, 4** keep the penis off the floor.”

**Spindle muscle control**

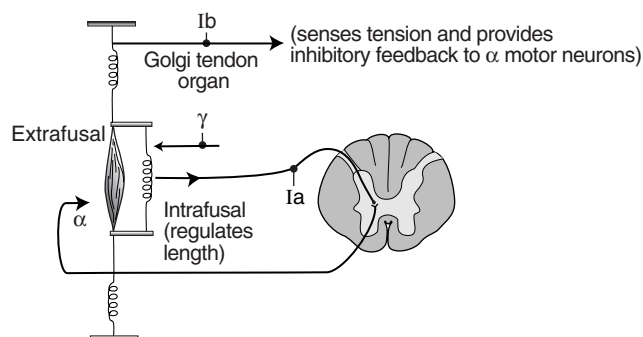
Muscle spindle

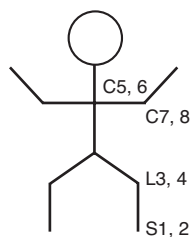
In parallel with muscle fibers. Muscle stretch → intrafusal stretch → stimulates Ia afferent → stimulates  $\alpha$  motor neuron → reflex muscle (extrafusal) contraction.

Gamma loop

CNS stimulates  $\gamma$  motor neuron → contracts intrafusal fiber → increased sensitivity of reflex arc.

Muscle spindles monitor muscle length (help you pick up a heavy suitcase when you didn't know how heavy it was). Golgi tendon organs monitor muscle tension (make you drop a heavy suitcase you've been holding too long).



**Clinical reflexes**

Biceps = C5 nerve root.

Triceps = C7 nerve root.

Patella = L4 nerve root.

Achilles = S1 nerve root.

Babinski—dorsiflexion of the big toe and fanning of other toes; sign of UMN lesion, but normal reflex in 1st year of life.

Reflexes count up in order:

S1, 2

L3, 4

C5, 6

C7, 8

**Primitive reflexes**

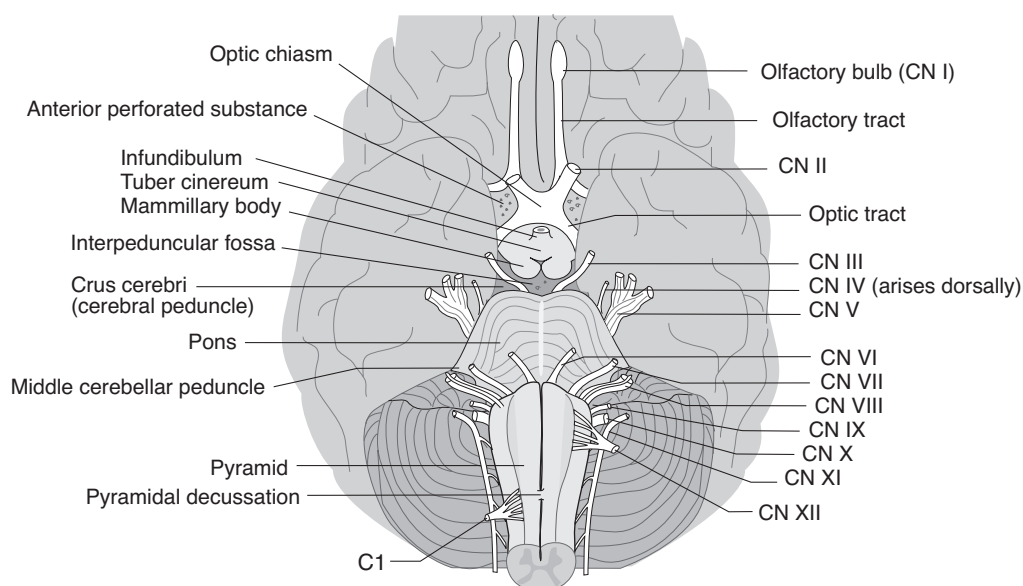
1. Moro reflex—extension of limbs when startled

2. Rooting reflex—nipple seeking

3. Palmar reflex—grasps objects in palm

4. Babinski reflex—large toe dorsiflexes with plantar stimulation

Normally disappear within 1st year. May reemerge following frontal lobe lesion.

**Brain stem anatomy**

CNs that lie medially at brain stem: III, VI, XII.  $3(\times 2) = 6(\times 2) = 12$ .



**Cranial nerves**

Nerve	CN	Function	Type	Mnemonic
Olfactory	I	Smell	Sensory	Some
Optic	II	Sight	Sensory	Say
Oculomotor	III	Eye movement, pupil constriction, accommodation, eyelid opening	Motor	Marry
Trochlear	IV	Eye movement	Motor	Money
Trigeminal	V	Mastication, facial sensation	Both	But
Abducens	VI	Eye movement	Motor	My
Facial	VII	Facial movement, taste from anterior $\frac{2}{3}$ of tongue, lacrimation, salivation (submaxillary and sublingual glands), eyelid closing	Both	Brother
Vestibulocochlear	VIII	Hearing, balance	Sensory	Says
Glossopharyngeal	IX	Taste from posterior $\frac{1}{3}$ of tongue, swallowing, salivation (parotid gland), monitoring carotid body and sinus chemo- and baroreceptors	Both	Big
Vagus	X	Taste from epiglottic region, swallowing, palate elevation, talking, thoracoabdominal viscera, monitoring aortic arch chemo- and baroreceptors	Both	Brains
Accessory	XI	Head turning, shoulder shrugging	Motor	Matter
Hypoglossal	XII	Tongue movement	Motor	Most

<b>Cranial nerve nuclei</b>	Located in tegmentum portion of brain stem (between dorsal and ventral portions). 1. Midbrain—nuclei of CN III, IV. 2. Pons—nuclei of CN V, VI, VII, VIII. 3. Medulla—nuclei of CN IX, X, XI, XII.	Lateral nuclei = sensory. Medial nuclei = <b>Motor</b> .
-----------------------------	-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	-------------------------------------------------------------

**Vagal nuclei**

Nucleus Solitarius	Visceral Sensory information (e.g., taste, baroreceptors, gut distention).	VII, IX, X.
Nucleus ambiguus	Motor innervation of pharynx, larynx, and upper esophagus (e.g., swallowing, palate elevation).	IX, X, XI.
Dorsal motor nucleus	Sends autonomic (parasympathetic) fibers to heart, lungs, and upper GI.	

**Cranial nerve and vessel pathways**

Cribriform plate (CN I).

Middle cranial fossa (CN II–VI)—through sphenoid bone:

1. Optic canal (CN II, ophthalmic artery, central retinal vein)
2. Superior orbital fissure (CN III, IV, V<sub>1</sub>, VI, ophthalmic vein)
3. Foramen Rotundum (CN V<sub>2</sub>)
4. Foramen Ovale (CN V<sub>3</sub>)
5. Foramen spinosum (middle meningeal artery)

Posterior cranial fossa (CN VII–XII)—through temporal or occipital bone:

1. Internal auditory meatus (CN VII, VIII)
2. Jugular foramen (CN IX, X, XI, jugular vein)
3. Hypoglossal canal (CN XII)
4. Foramen magnum (spinal roots of CN XI, brain stem, vertebral arteries)

Divisions of CN V exit owing to Standing Room Only.

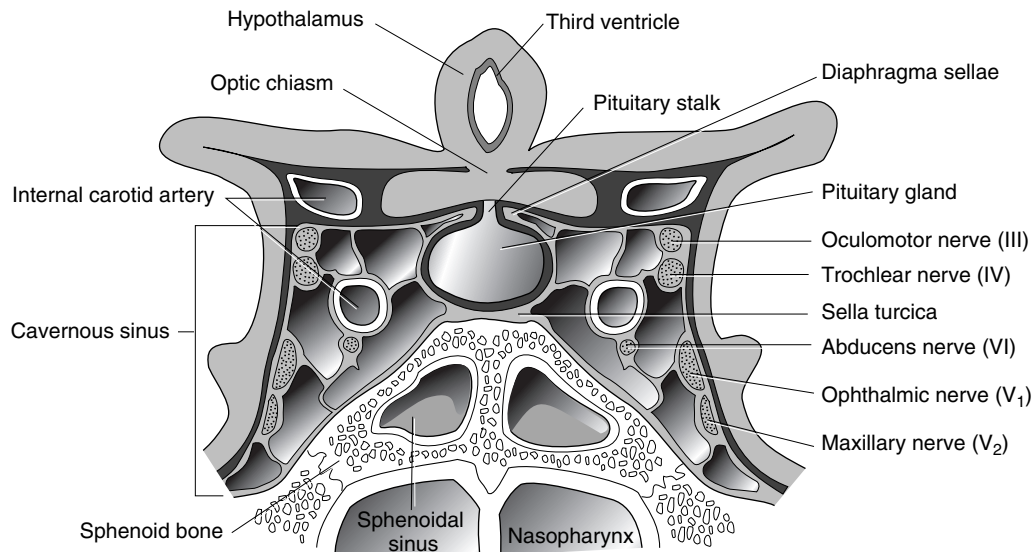
**Cavernous sinus**

A collection of venous sinuses on either side of the pituitary. Blood from eye and superficial cortex → cavernous sinus → internal jugular vein.

CN III, IV, V<sub>1</sub>, V<sub>2</sub>, and VI and postganglionic sympathetic fibers en route to the orbit all pass through the cavernous sinus. Only CN VI is “free-floating.” Cavernous portion of internal carotid artery is also here.

The nerves that control extraocular muscles (plus V<sub>1</sub> and V<sub>2</sub>) pass through the cavernous sinus.

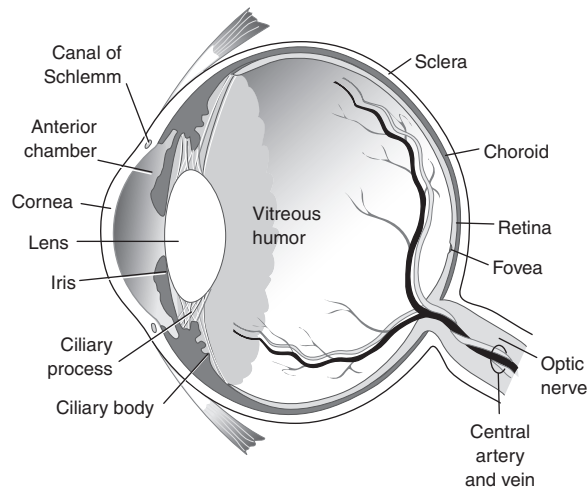
Cavernous sinus syndrome (e.g., due to mass effect)—ophthalmoplegia, ophthalmic and maxillary sensory loss.



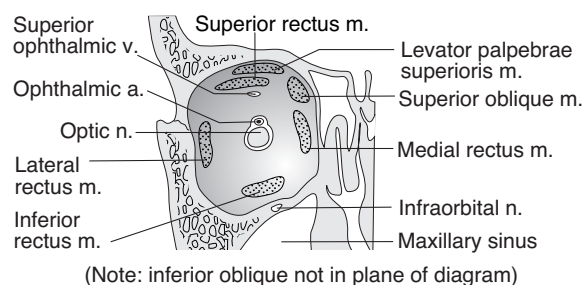
(Adapted, with permission, from Stobo J et al. *The Principles and Practice of Medicine*, 23rd ed. Stamford, CT: Appleton & Lange, 1996:277.)

<b>Mastication muscles</b>	3 muscles close jaw: <b>M</b> asseter, <b>t</b> emporalis, <b>M</b> edial pterygoid. 1 opens: lateral pterygoid. All are innervated by the trigeminal nerve ( $V_3$ ).	<b>M's Munch.</b> <b>L</b> ateral <b>L</b> owers (when speaking of pterygoids with respect to jaw motion).
<b>Muscles with glossus</b>	All muscles with root <i>glossus</i> in their names ( <b>except palatoglossus</b> , innervated by vagus nerve) are innervated by hypoglossal nerve.	<i>Palat</i> : vagus nerve. <i>Glossus</i> : hypoglossal nerve.
<b>Muscles with palat</b>	All muscles with root <i>palat</i> in their names ( <b>except tensor veli palatini</b> , innervated by mandibular branch of CN V) are innervated by vagus nerve.	<i>Palat</i> : vagus nerve (except <b>TENS</b> or, who was too <b>TENSE</b> ).

## Eye and retina

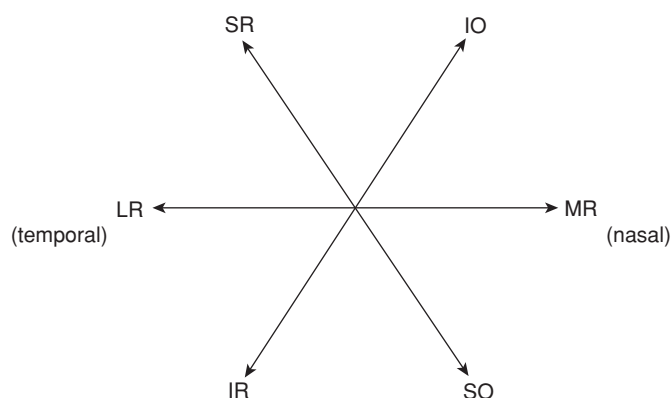


## Extraocular muscles and nerves



CN VI innervates the **L**ateral **R**ectus.  
 CN IV innervates the **S**uperior **O**blique.  
 CN III innervates the **R**est.  
 The “chemical formula” **LR<sub>6</sub>SO<sub>4</sub>R<sub>3</sub>**.  
 The superior oblique abducts, introverts, depresses.

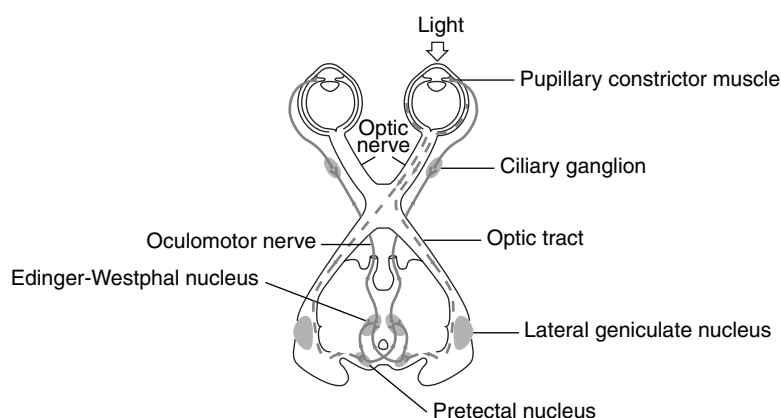
## Testing extraocular muscles



## Pupillary light reflex

Light in either retina sends a signal via CN II to pretectal nuclei (dashed lines) in midbrain that activate bilateral Edinger-Westphal nuclei; pupils contract bilaterally (consensual reflex).

Note that the illumination of 1 eye results in bilateral pupillary constriction.

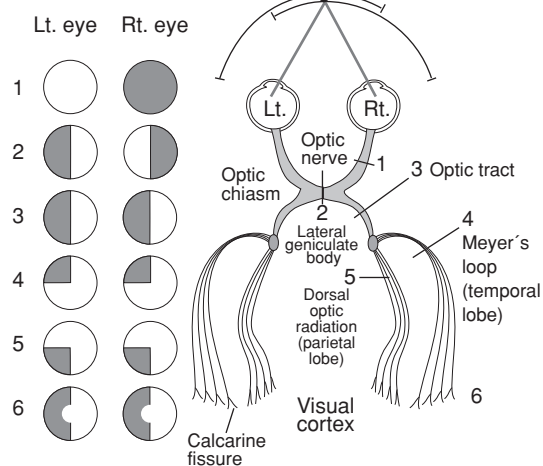


(Adapted, with permission, from Simon RP et al. *Clinical Neurology*, 3rd ed. Stamford, CT: Appleton & Lange, 1996.)

## Visual field defects

1. Right anopia
2. Bitemporal hemianopia
3. Left homonymous hemianopia
4. Left upper quadrantic anopia (right temporal lesion)
5. Left lower quadrantic anopia (right parietal lesion)
6. Left hemianopia with macular sparing

### Defect in visual field of



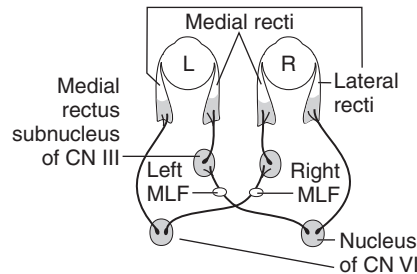
► **NEUROLOGY—ANATOMY AND PHYSIOLOGY (continued)**

**Internuclear ophthalmoplegia (MLF syndrome)**

Lesion in the medial longitudinal fasciculus (MLF). Results in medial rectus palsy on attempted lateral gaze. Nystagmus in abducting eye. Convergence is normal. MLF syndrome is seen in many patients with multiple sclerosis.

**MLF = MS.**

When looking left, the left nucleus of CN VI fires, which contracts the left lateral rectus and stimulates the contralateral (right) nucleus of CN III via the right MLF to contract the right medial rectus.



**KLM sounds: kuh, la, mi**

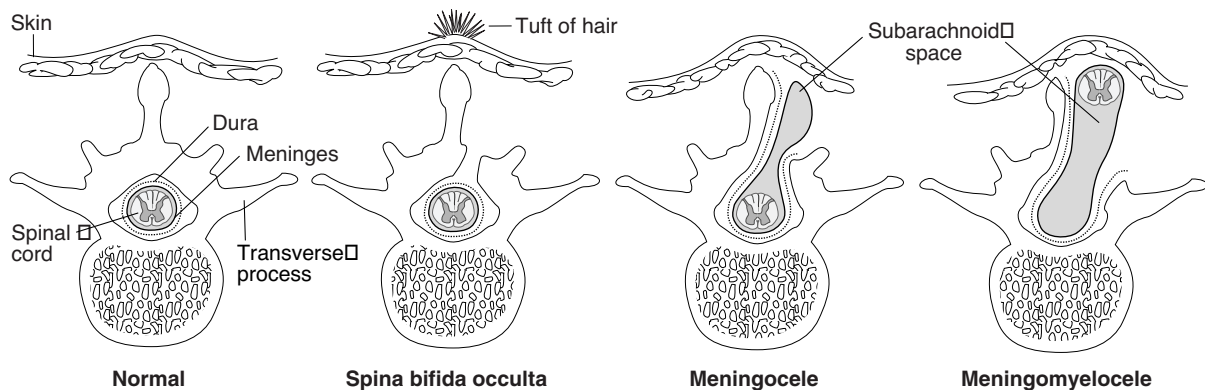
Kuh-kuh-kuh tests palate elevation (CN X—vagus).  
La-la-la tests tongue (CN XII—hypoglossal).  
Mi-mi-mi tests lips (CN VII—facial).

Say it aloud.

► **NEUROLOGY—PATHOLOGY**

**Neural tube defects**

Associated with low folic acid intake during pregnancy. Elevated  $\alpha$ -fetoprotein in amniotic fluid and maternal serum.  
Spina bifida occulta—failure of bony spinal canal to close, but no structural herniation. Usually seen at lower vertebral levels.  
Meningocele—meninges herniate through spinal canal defect.  
Meningomyelocele—meninges and spinal cord herniate through spinal canal defect.



**Brain lesions**

Area of lesion	Consequence	
Broca's area	Motor (nonfluent/expressive) aphasia with good comprehension	<b>BRO</b> ca's is <b>BRO</b> ken speech.
Wernicke's area	Sensory (fluent/receptive) aphasia with poor comprehension	<b>W</b> ernicke's is <b>W</b> ordy but makes no sense.
Arcuate fasciculus	Conduction aphasia; poor repetition with good comprehension, fluent speech	Connects Wernicke's to Broca's area.
Amygdala (bilateral)	Klüver-Bucy syndrome (hyperorality, hypersexuality, disinhibited behavior)	
Frontal lobe	Personality changes and deficits in concentration, orientation, and judgment; may have reemergence of primitive reflexes	
Right parietal lobe	Spatial neglect syndrome (agnosia of the contralateral side of the world)	
Reticular activating system	Coma	
Mammillary bodies (bilateral)	Wernicke-Korsakoff syndrome	
Basal ganglia	May result in tremor at rest, chorea, or athetosis	
Cerebellar hemisphere	Intention tremor, limb ataxia	Cerebellar hemispheres are <b>laterally</b> located—affect <b>lateral</b> limbs. Vermis is <b>centrally</b> located—affects <b>central</b> body.
Cerebellar vermis	Truncal ataxia, dysarthria	
Subthalamic nucleus	Contralateral hemiballismus	
<b>Chorea</b>	Sudden, jerky, purposeless movements. Characteristic of basal ganglia lesion (e.g., Huntington's disease).	<i>Chorea</i> = dancing (Greek). Think choral dancing or choreography.
<b>Athetosis</b>	Slow, writhing movements, especially of fingers. Characteristic of basal ganglia lesion.	<i>Athetos</i> = not fixed (Greek). Think snakelike.
<b>Hemiballismus</b>	Sudden, wild flailing of 1 arm. Characteristic of contralateral subthalamic nucleus lesion. Loss of inhibition of thalamus through globus pallidus.	Half ballistic (as in throwing a baseball).
<b>Aphasia</b>		
Broca's	Nonfluent aphasia with intact comprehension. Broca's area—inferior frontal gyrus.	<b>Bro</b> ca's is <b>Br</b> oken speech;
Wernicke's	Fluent aphasia with impaired comprehension. Wernicke's area—superior temporal gyrus.	<b>W</b> ernicke's is <b>W</b> ordy but makes no sense. <b>W</b> ernicke's = "What?"

**Degenerative diseases**

Cerebral cortex	<p><b>Alzheimer's disease</b>—most common cause of dementia in the elderly. Associated with senile plaques (extracellular, <math>\beta</math>-amyloid core) and neurofibrillary tangles (intracellular, abnormally phosphorylated tau protein). Familial form (10%) associated with genes on chromosomes 1, 14, 19 (<i>APOE4</i> allele), and 21 (<i>p-Ap</i> gene) (see Color Image 41).</p>	<p>Multi-infarct dementia is the 2nd most common cause of dementia in the elderly. May cause amyloid angiopathy → intracranial hemorrhage.</p>
Basal ganglia and brain stem	<p><b>Pick's disease</b>—dementia, aphasia, parkinsonian aspects; associated with Pick bodies (intracellular, aggregated tau protein) and is specific for the frontal and temporal lobes.</p> <p><b>Huntington's disease</b>—autosomal-dominant inheritance, chorea, dementia. Atrophy of caudate nucleus (loss of GABAergic neurons).</p> <p><b>Parkinson's disease</b>—associated with Lewy bodies and depigmentation of the substantia nigra pars compacta (loss of dopaminergic neurons). Rare cases have been linked to exposure to MPTP, a contaminant in illicit street drugs.</p>	<p>Chromosome 4—expansion of CAG repeats. <b>CAG</b>—Caudate loses ACh and GABA.</p> <p><b>TRAP</b> = Tremor (at rest), cogwheel <b>R</b>igidity, <b>A</b>kinesia, and <b>P</b>ostural instability (you are <b>TRAP</b>ped in your body).</p>
Spinocerebellar Motor neuron	<p><b>Olivopontocerebellar atrophy; Friedreich's ataxia.</b></p> <p><b>Amyotrophic lateral sclerosis (ALS)</b>—associated with both LMN and UMN signs; no sensory deficit. Can be caused by defect in SOD1.</p> <p><b>Werdnig-Hoffmann disease</b>—autosomal-recessive inheritance; presents at birth as a “floppy baby,” tongue fasciculations; median age of death 7 months. Associated with degeneration of anterior horns.</p> <p><b>Polio</b>—follows infection with poliovirus; LMN signs. Associated with degeneration of anterior horns.</p>	<p>Commonly known as Lou Gehrig's disease.</p>
<b>Poliomyelitis</b>	<p>Caused by poliovirus, which is transmitted by the fecal-oral route. Replicates in the oropharynx and small intestine before spreading through the bloodstream to the CNS, where it leads to the destruction of cells in the anterior horn of the spinal cord, leading in turn to LMN destruction.</p>	
Symptoms	<p>Malaise, headache, fever, nausea, abdominal pain, sore throat. Signs of LMN lesions—muscle weakness and atrophy, fasciculations, fibrillation, and hyporeflexia.</p>	
Findings	<p>CSF with lymphocytic pleocytosis with slight elevation of protein. Virus recovered from stool or throat.</p>	

<b>Demyelinating and dysmyelinating diseases</b>	<ol style="list-style-type: none"> <li>1. Multiple sclerosis (MS)—↑ prevalence with ↑ distance from the equator; periventricular plaques (areas of oligodendrocyte loss and reactive gliosis) with preservation of axons; ↑ protein (IgG) in CSF. Many patients have a relapsing-remitting course. Patients can present with optic neuritis (sudden loss of vision), MLF syndrome (internuclear ophthalmoplegia), hemiparesis, hemisensory symptoms, or bladder/bowel incontinence (see Color Image 47).</li> <li>2. Progressive multifocal leukoencephalopathy (PML)—associated with JC virus and seen in 2–4% of AIDS patients (reactivation of latent viral infection).</li> <li>3. Acute disseminated (postinfectious) encephalomyelitis.</li> <li>4. Metachromatic leukodystrophy (a lysosomal storage disease).</li> <li>5. Guillain-Barré syndrome (see below).</li> </ol>	<p>Classic triad of MS is a <b>SIN</b>:</p> <ul style="list-style-type: none"> <li>Scanning speech</li> <li>Intention tremor</li> <li>Nystagmus</li> </ul> <p>Most often affects women in their 20s and 30s; more common in whites.</p> <p>Treatment: β-interferon or immunosuppressant therapy.</p>
<b>Guillain-Barré syndrome (acute idiopathic polyneuritis)</b>	<p>Inflammation and demyelination of peripheral nerves and motor fibers of ventral roots (sensory effect less severe than motor), causing symmetric ascending muscle weakness beginning in distal lower extremities. Facial diplegia in 50% of cases. Autonomic function may be severely affected (e.g., cardiac irregularities, hypertension, or hypotension). Almost all patients survive; the majority recover completely after weeks to months.</p> <p>Findings: elevated CSF protein with normal cell count (“albuminocytologic dissociation”).</p> <p>Elevated protein → papilledema.</p>	<p>Associated with infections → immune attack of peripheral myelin (e.g., herpesvirus or <i>Campylobacter jejuni</i> infection), inoculations, and stress, but no definitive link to pathogens.</p> <p>Respiratory support is critical until recovery. Additional treatment: plasmapheresis, IV immune globulins.</p>
<b>Seizures</b>	<p>Partial seizures—1 area of the brain.</p> <ol style="list-style-type: none"> <li>1. Simple partial (consciousness intact)—motor, sensory, autonomic, psychic</li> <li>2. Complex partial (impaired consciousness)</li> </ol> <p>Generalized seizures—diffuse.</p> <ol style="list-style-type: none"> <li>1. Absence (petit mal)—blank stare</li> <li>2. Myoclonic—quick, repetitive jerks</li> <li>3. Tonic-clonic (grand mal)—alternating stiffening and movement</li> <li>4. Tonic—stiffening</li> <li>5. Atonic—“drop” seizures</li> </ol>	<p>Epilepsy is a disorder of recurrent seizures (febrile seizures are not epilepsy).</p> <p>Partial seizures can secondarily generalize.</p> <p>Causes of seizures by age:</p> <ul style="list-style-type: none"> <li>Children—genetic, infection, trauma, congenital, metabolic.</li> <li>Adults—tumors, trauma, stroke, infection.</li> <li>Elderly—stroke, tumor, trauma, metabolic, infection.</li> </ul>



**Intracranial hemorrhage**

Epidural hematoma	Rupture of middle meningeal artery, often 2° to fracture of temporal bone. Lucid interval (see Color Image 44).	CT shows “biconvex disk” not crossing suture lines.
Subdural hematoma	Rupture of bridging veins. Venous bleeding (less pressure) with delayed onset of symptoms. Seen in elderly individuals, alcoholics, blunt trauma, shaken baby (predisposing factors—brain atrophy, shaking, whiplash) (see Color Image 43).	Crescent-shaped hemorrhage that crosses suture lines.
Subarachnoid hemorrhage	Rupture of an aneurysm (usually berry aneurysm) or an AVM. Patients complain of “worst headache of my life.” Bloody or xanthochromic spinal tap.	
Parenchymal hematoma	Caused by hypertension, amyloid angiopathy, diabetes mellitus, and tumor.	

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<b>Berry aneurysms</b>	Berry aneurysms occur at the bifurcations in the circle of Willis. Most common site is bifurcation of the anterior communicating artery. Rupture (most common complication) leads to hemorrhagic stroke/subarachnoid hemorrhage. Associated with adult polycystic kidney disease, Ehlers-Danlos syndrome, and Marfan’s syndrome. Other risk factors: advanced age, hypertension, smoking, race (higher risk in blacks) (see Color Image 46).
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**Primary brain tumors**

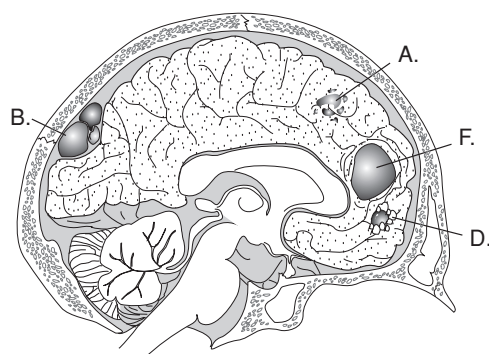
Clinical presentation due to mass effects (e.g., seizures, dementia, focal lesions); 1° brain tumors rarely undergo metastasis. The majority of adult 1° tumors are supratentorial, while the majority of childhood 1° tumors are infratentorial. Note: half of adult brain tumors are metastases.

**Adult peak incidence**

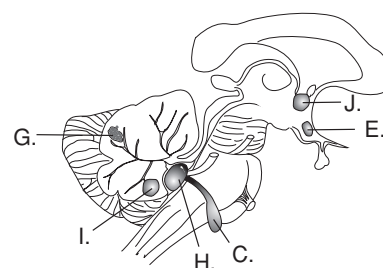
- |                                                   |                                                                                                                                                                                                        |                                                                                                               |
|---------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------|
| A. Glioblastoma multiforme (grade IV astrocytoma) | Most common 1° brain tumor. Prognosis grave; < 1-year life expectancy. Found in cerebral hemispheres. Can cross corpus callosum (“butterfly glioma”) (see Color Image 48). Stain astrocytes with GFAP. | “Pseudopalisading” tumor cells—border central areas of necrosis and hemorrhage.                               |
| B. Meningioma                                     | 2nd most common 1° brain tumor. Most often occurs in convexities of hemispheres and parasagittal region. Arises from arachnoid cells external to brain. Resectable.                                    | Spindle cells concentrically arranged in a whorled pattern; psammoma bodies (laminated calcifications).       |
| C. Schwannoma                                     | 3rd most common 1° brain tumor. Schwann cell origin; often localized to 8th nerve → acoustic schwannoma. Resectable.                                                                                   | Bilateral schwannoma found in neurofibromatosis type 2.                                                       |
| D. Oligodendroglioma                              | Relatively rare, slow growing. Most often in frontal lobes (see Color Image 49).                                                                                                                       | Oligodendrocytes = “fried egg” cells—round nuclei with clear cytoplasm. Often calcified in oligodendroglioma. |
| E. Pituitary adenoma                              | Prolactin secreting is most common form. Bitemporal hemianopia (due to pressure on optic chiasm) and hyper- or hypopituitarism are sequelae.                                                           | Rathke’s pouch.                                                                                               |

**Childhood peak incidence**

- |                                      |                                                                                                                                             |                                                                                                                  |
|--------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------|
| F. Pilocytic (low-grade) astrocytoma | Diffusely infiltrating glioma. In children, most often found in posterior fossa. Benign; good prognosis.                                    | Rosenthal fibers—eosinophilic, corkscrew fibers.                                                                 |
| G. Medulloblastoma                   | Highly malignant cerebellar tumor. A form of primitive neuroectodermal tumor (PNET). Can compress 4th ventricle, causing hydrocephalus.     | Rosettes or perivascular pseudorosette pattern of cells. Radiosensitive.                                         |
| H. Ependymoma                        | Ependymal cell tumors most commonly found in 4th ventricle. Can cause hydrocephalus. Poor prognosis.                                        | Characteristic perivascular pseudorosettes. Rod-shaped blepharoplasts (basal ciliary bodies) found near nucleus. |
| I. Hemangioblastoma                  | Most often cerebellar; associated with von Hippel-Lindau syndrome when found with retinal angiomas. Can produce EPO → 2° polycythemia.      | Foamy cells and high vascularity are characteristic.                                                             |
| J. Craniopharyngioma                 | Benign childhood tumor, confused with pituitary adenoma (can also cause bitemporal hemianopia). Most common childhood supratentorial tumor. | Derived from remnants of Rathke’s pouch. Calcification is common.                                                |



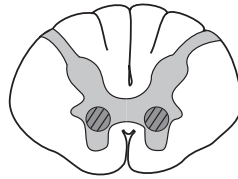
Supratentorial



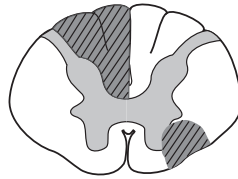
Infratentorial

## Spinal cord lesions

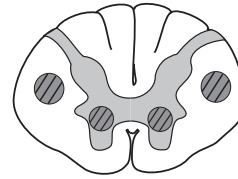
Poliomyelitis and Werdnig-Hoffmann disease: lower motor neuron lesions only, due to destruction of anterior horns; flaccid paralysis



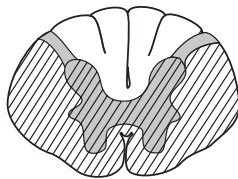
Multiple sclerosis: mostly white matter of cervical region; random and asymmetric lesions, due to demyelination; scanning speech, intention tremor, nystagmus



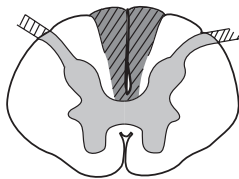
ALS: combined upper and lower motor neuron deficits with no sensory deficit; both upper and lower motor neuron signs



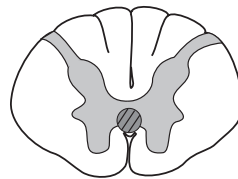
Complete occlusion of ventral artery; spares dorsal columns and tract of Lissauer



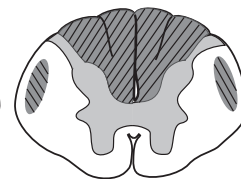
Tabes dorsalis (3° syphilis): degeneration of dorsal roots and dorsal columns; impaired proprioception, locomotor ataxia



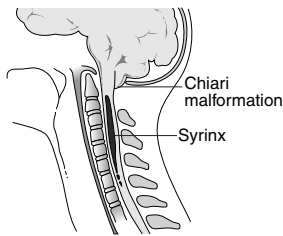
Syringomyelia: crossing fibers of spinothalamic tract damaged; bilateral loss of pain and temperature sensation



Vitamin B<sub>12</sub> neuropathy and Friedreich's ataxia: demyelination of dorsal columns, lateral corticospinal tracts, and spinocerebellar tracts; ataxic gait, hyperreflexia, impaired position and vibration sense



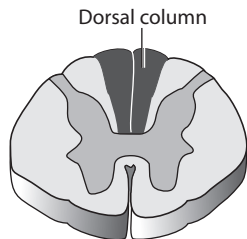
### Syringomyelia



Enlargement of the central canal of spinal cord. Crossing fibers of spinothalamic tract are damaged. Bilateral loss of pain and temperature sensation in upper extremities with preservation of touch sensation.

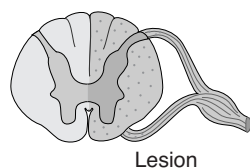
*Syrinx* (Greek) = tube, as in syringe. Often presents in patients with Arnold-Chiari malformation. Most common at C8–T1.

### Tabes dorsalis



Degeneration of dorsal columns and dorsal roots due to 3° syphilis, resulting in impaired proprioception and locomotor ataxia. Associated with Charcot's joints, shooting (lightning) pain, Argyll Robertson pupils (reactive to accommodation but not to light), and absence of DTRs.

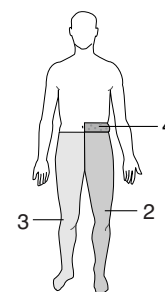
## Brown-Séquard syndrome



Hemisection of spinal cord. Findings:

1. Ipsilateral UMN signs (corticospinal tract) below lesion—not shown
2. Ipsilateral loss of tactile, vibration, proprioception sense (dorsal column) below lesion
3. Contralateral pain and temperature loss (spinothalamic tract) below lesion
4. Ipsilateral loss of all sensation at level of lesion
5. LMN signs at level of lesion

If lesion occurs above T1, presents with Horner's syndrome.



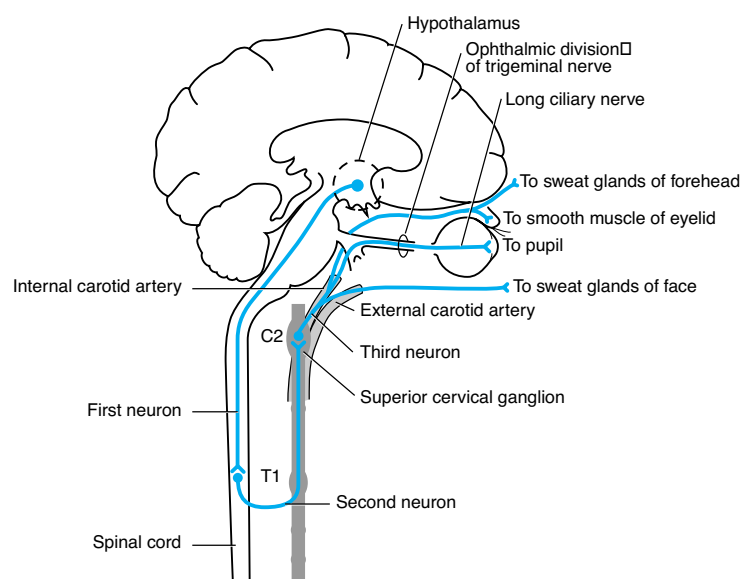
## Horner's syndrome

Sympathectomy of face:

1. Ptosis (slight drooping of eyelid)
2. Anhidrosis (absence of sweating) and flushing (rubor) of affected side of face
3. Miosis (pupil constriction)

Associated with lesion of spinal cord above T1 (e.g., Pancoast's tumor, hemisection, late-stage syringomyelia).

PAM is horny.



(Adapted, with permission, from Simon RP et al. *Clinical Neurology*, 4th ed. Stamford, CT: Appleton & Lange, 1999:146.)

The 3-neuron oculosympathetic pathway above projects from the hypothalamus to the intermediolateral column of the spinal cord, then to the superior cervical (sympathetic) ganglion, and finally to the pupil, the smooth muscle of the eyelids, and the sweat glands of the forehead and face. Interruption of these pathways results in Horner's syndrome.

**Cranial nerve and cerebellar lesions**

CN XII lesion (LMN)—tongue deviates **toward** side of lesion (lick your wounds).  
 CN V motor lesion—jaw deviates **toward** side of lesion.  
 Unilateral lesion of cerebellum—patient tends to fall **toward** side of lesion.  
 CN X lesion—uvula deviates **away** from side of lesion.  
 CN XI lesion—weakness turning head to contralateral side of lesion. Shoulder droop on side of lesion.

**Facial lesions**

UMN lesion

Lesion of motor cortex or connection between cortex and facial nucleus.  
 Contralateral paralysis of lower face only.

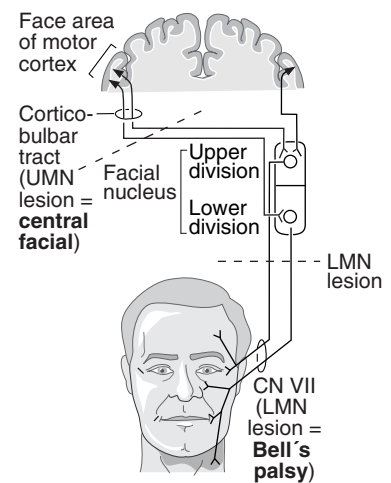
LMN lesion

Ipsilateral paralysis of upper and lower face.  
 Complete destruction of the facial nucleus itself or its branchial efferent fibers (facial nerve proper).

Bell's palsy

Peripheral ipsilateral facial paralysis with inability to close eye on involved side.  
 Can occur idiopathically; gradual recovery in most cases.  
 Seen as a complication in AIDS, Lyme disease, Sarcoidosis, Tumors, Diabetes.

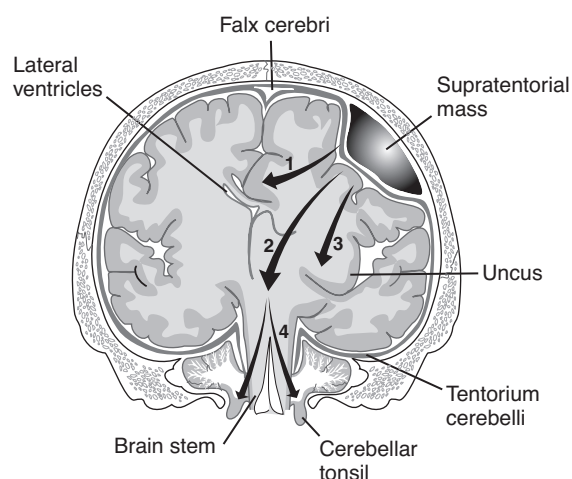
**ALexander Bell with STD:**  
 AIDS, Lyme, Sarcoid, Tumors, Diabetes.



**Motor neuron signs**

Sign	UMN lesion	LMN lesion	
Weakness	+	+	<b>Lower MN = everything lowered</b> (less muscle mass, ↓ muscle tone, ↓ reflexes, downgoing toes).
Atrophy	–	+	
Fasciculation	–	+	<b>Upper MN = everything up</b> (tone, DTRs, toes).
Reflexes	↑	↓	
Tone	↑	↓	
Babinski	+	–	

## Herniation syndromes



1. Cingulate herniation under falx cerebri
2. Downward transtentorial (central) herniation
3. Uncal herniation
4. Cerebellar tonsillar herniation into the foramen magnum

Can compress anterior cerebral artery.  
Coma and death result when these herniations compress the brain stem.  
Uncus = medial temporal lobe.

(Adapted, with permission, from Simon RP et al. *Clinical Neurology*, 4th ed. Stamford, CT: Appleton & Lange, 1999:314.)

### Uncal herniation

Clinical signs	Cause
Ipsilateral dilated pupil/ptosis	Stretching of CN III
Contralateral homonymous hemianopia	Compression of ipsilateral posterior cerebral artery
Ipsilateral paresis	Compression of contralateral crus cerebri (Kernohan's notch)
Duret hemorrhages—paramedian artery rupture	Caudal displacement of brain stem

## ► NEUROLOGY—PHARMACOLOGY

### Parkinson's disease drugs

Parkinsonism is due to loss of dopaminergic neurons and excess cholinergic activity.

Strategy	Agents
Agonize dopamine receptors	Bromocriptine (ergot alkaloid and partial dopamine agonist), pramipexole, ropinirole
Increase dopamine	Amantadine (may ↑ dopamine release) L-dopa/carbidopa (converted to dopamine in CNS)
Prevent dopamine breakdown	Selegiline (selective MAO type B inhibitor); entacapone, tolcapone (COMT inhibitors)
Curb excess cholinergic activity	Benztrapine (Antimuscarinic; improves tremor and rigidity but has little effect on bradykinesia)

### BALSA:

Bromocriptine  
Amantadine  
Levodopa (with carbidopa)  
Selegiline (and COMT inhibitors)  
Antimuscarinics

**L-dopa (levodopa)/carbidopa**

Mechanism	↑ level of dopamine in brain. Unlike dopamine, L-dopa can cross blood-brain barrier and is converted by dopa decarboxylase in the CNS to dopamine.
Clinical use	Parkinsonism.
Toxicity	Arrhythmias from peripheral conversion to dopamine. Carbidopa, a peripheral decarboxylase inhibitor, is given with L-dopa in order to ↑ the bioavailability of L-dopa in the brain and to limit peripheral side effects. Long-term use can → dyskinesia following administration, akinesia between doses.

**Selegiline**

Mechanism	Selectively inhibits MAO-B, thereby ↑ the availability of dopamine.
Clinical use	Adjunctive agent to L-dopa in treatment of Parkinson's disease.
Toxicity	May enhance adverse effects of L-dopa.

**Sumatriptan**

Mechanism	5-HT <sub>1D</sub> agonist. Causes vasoconstriction. Half-life < 2 hours.
Clinical use	Acute migraine, cluster headache attacks.
Toxicity	Coronary vasospasm, mild tingling (contraindicated in patients with CAD or Prinzmetal's angina).

## Epilepsy drugs

	PARTIAL		GENERALIZED			Mechanism	Notes
	Simple	Complex	Tonic-Clonic	Absence	Status		
Phenytoin	✓	✓	1st line		1st line for prophylaxis	↑ Na <sup>+</sup> channel inactivation	
Carbamazepine	✓	✓	1st line			↑ Na <sup>+</sup> channel inactivation	1st line for trigeminal neuralgia
Lamotrigine	✓	✓	✓			Blocks voltage-gated Na <sup>+</sup> channels	
Gabapentin	✓	✓	✓			↑ GABA release	Also used for peripheral neuropathy
Topiramate	✓	✓	✓			Blocks Na <sup>+</sup> channels, ↑ GABA action	
Phenobarbital	✓	✓	✓			↑ GABA <sub>A</sub> action	1st line in pregnant women, children
Valproic acid	✓	✓	1st line	✓		↑ Na <sup>+</sup> channel inactivation, ↑ GABA concentration	Also used for myoclonic seizures
Ethosuximide				1st line		Blocks thalamic T-type Ca <sup>2+</sup> channels	
Benzodiazepines (diazepam or lorazepam)					1st line for acute	↑ GABA <sub>A</sub> action	Also used for seizures of eclampsia (1st line to prevent seizures of eclampsia is MgSO <sub>4</sub> )

## Epilepsy drug toxicities

Benzodiazepines	Sedation, tolerance, dependence.
Carbamazepine	Diplopia, ataxia, blood dyscrasias (agranulocytosis, aplastic anemia), liver toxicity, teratogenesis, induction of cytochrome P-450.
Ethosuximide	GI distress, lethargy, headache, urticaria, Stevens-Johnson syndrome.
Phenobarbital	Sedation, tolerance, dependence, induction of cytochrome P-450.
Phenytoin	Nystagmus, diplopia, ataxia, sedation, gingival hyperplasia, hirsutism, megaloblastic anemia, teratogenesis, SLE-like syndrome, induction of cytochrome P-450.
Valproic acid	GI distress, rare but fatal hepatotoxicity (measure LFTs), neural tube defects in fetus (spina bifida), tremor, weight gain.
Lamotrigine	Stevens-Johnson syndrome.
Gabapentin	Sedation, ataxia.
Topiramate	Sedation, mental dulling, kidney stones, weight loss.



**Phenytoin**

Mechanism	Use-dependent blockade of Na <sup>+</sup> channels; inhibition of glutamate release from excitatory presynaptic neuron.
Clinical use	Tonic-clonic seizures. Also a class IB antiarrhythmic.
Toxicity	Nystagmus, ataxia, diplopia, sedation, SLE-like syndrome, induction of cytochrome P-450. Chronic use produces gingival hyperplasia in children, peripheral neuropathy, hirsutism, megaloblastic anemia (↓ folate absorption), and malignant hyperthermia (rare); teratogenic (fetal hydantoin syndrome).

**Barbiturates**

Mechanism	Phenobarbital, pentobarbital, thiopental, secobarbital. Facilitate GABA <sub>A</sub> action by ↑ <b>duration</b> of Cl <sup>−</sup> channel opening, thus ↓ neuron firing.	Barbi <b>DUR</b> ATe (increased <b>DUR</b> ATion).
Clinical use	Sedative for anxiety, seizures, insomnia, induction of anesthesia (thiopental).	Contraindicated in porphyria.
Toxicity	Dependence, additive CNS depression effects with alcohol, respiratory or cardiovascular depression (can lead to death), drug interactions owing to induction of liver microsomal enzymes (cytochrome P-450). Treat overdose with symptom management (assist respiration, ↑ BP).	

**Benzodiazepines**

	Diazepam, lorazepam, triazolam, temazepam, oxazepam, midazolam, chlordiazepoxide, alprazolam.	
Mechanism	Facilitate GABA <sub>A</sub> action by ↑ <b>frequency</b> of Cl <sup>−</sup> channel opening. Most have long half-lives and active metabolites.	<b>FRE</b> nzodiazepines (increased <b>FRE</b> quency).
Clinical use	Anxiety, spasticity, status epilepticus (lorazepam and diazepam), detoxification (especially alcohol withdrawal–DTs), night terrors, sleepwalking.	Short acting = <b>TOM</b> Thumb = <b>Triazolam, Oxazepam, Midazolam</b> .
Toxicity	Dependence, additive CNS depression effects with alcohol. Less risk of respiratory depression and coma than with barbiturates. Treat overdose with flumazenil (competitive antagonist at GABA receptor).	

**Anesthetics—  
general principles**

CNS drugs must be lipid soluble (cross the blood-brain barrier) or be actively transported.  
 Drugs with ↓ solubility in blood = rapid induction and recovery times.  
 Drugs with ↑ solubility in lipids = ↑ potency =  $\frac{1}{\text{MAC}}$   
 where MAC = minimal anesthetic concentration.  
 Examples: N<sub>2</sub>O has low blood and lipid solubility, and thus fast induction and low potency. Halothane, in contrast, has ↑ lipid and blood solubility, and thus high potency and slow induction.

<b>Inhaled anesthetics</b>	
Mechanism	Halothane, enflurane, isoflurane, sevoflurane, methoxyflurane, nitrous oxide. Mechanism unknown.
Effects	Myocardial depression, respiratory depression, nausea/emesis, ↑ cerebral blood flow (↓ cerebral metabolic demand).
Toxicity	Hepatotoxicity (halothane), nephrotoxicity (methoxyflurane), proconvulsant (enflurane), malignant hyperthermia (rare).
<b>Intravenous anesthetics</b>	
Barbiturates	Thiopental—high potency, high lipid solubility, rapid entry into brain. Used for induction of anesthesia and short surgical procedures. Effect terminated by redistribution from brain. ↓ cerebral blood flow.
Benzodiazepines	Midazolam most common drug used for endoscopy; used adjunctively with gaseous anesthetics and narcotics. May cause severe postoperative respiratory depression, ↓ BP (treat with flumazenil), and amnesia.
Arylcyclohexamines (Ketamine)	PCP analogs that act as dissociative anesthetics. Cardiovascular stimulants. Cause disorientation, hallucination, and bad dreams. ↑ cerebral blood flow.
Opiates	Morphine, fentanyl used with other CNS depressants during general anesthesia.
Propofol	Used for rapid anesthesia induction and short procedures. Less postoperative nausea than thiopental.
<b>Local anesthetics</b>	
	Esters—procaine, cocaine, tetracaine; amides—lidocaine, mepivacaine, bupivacaine (amides have 2 I's in name).
Mechanism	Block Na <sup>+</sup> channels by binding to specific receptors on inner portion of channel. 3° amine local anesthetics penetrate membrane in uncharged form, then bind to ion channels as charged form.
Principle	<ol style="list-style-type: none"> <li>1. In infected (acidic) tissue, anesthetics are charged and cannot penetrate membrane effectively. Therefore, more anesthetic is needed in these cases.</li> <li>2. Order of nerve blockade—small-diameter fibers &gt; large diameter. Myelinated fibers &gt; unmyelinated fibers. Overall, size factor predominates over myelination such that very small unmyelinated pain fibers &gt; small myelinated autonomic fibers &gt; large myelinated autonomic fibers. Order of loss—pain (lose first) &gt; temperature &gt; touch &gt; pressure (lose last).</li> <li>3. Given with vasoconstrictors (usually epinephrine) to enhance local action—↓ bleeding, ↑ anesthesia by ↓ systemic concentration.</li> </ol>
Clinical use	Minor surgical procedures, spinal anesthesia. If allergic to esters, give amides.
Toxicity	CNS excitation, severe cardiovascular toxicity (bupivacaine), hypertension, hypotension, and arrhythmias (cocaine).

**B. B. King on OPIATES**  
**PROPO**ses **FOOL**ishly.

**Neuromuscular blocking drugs**

Depolarizing

Used for muscle paralysis in surgery or mechanical ventilation. Selective for motor (vs. autonomic) nicotinic receptor.

Succinylcholine.

Reversal of blockade:

Phase I (prolonged depolarization)—no antidote. Block potentiated by cholinesterase inhibitors.

Phase II (repolarized but blocked)—antidote consists of cholinesterase inhibitors (e.g., neostigmine).

Nondepolarizing

Tubocurarine, atracurium, mivacurium, pancuronium, vecuronium, rapacuronium.

Competitive—compete with ACh for receptors.

Reversal of blockade—neostigmine, edrophonium, and other cholinesterase inhibitors.

**Dantrolene**

Used in the treatment of **malignant hyperthermia**, which is caused by the concomitant use of inhalation anesthetics (except N<sub>2</sub>O) and succinylcholine. Also used to treat **neuroleptic malignant syndrome** (a toxicity of antipsychotic drugs).

Mechanism: prevents the release of Ca<sup>2+</sup> from the sarcoplasmic reticulum of skeletal muscle.

# HIGH-YIELD PRINCIPLES IN

# Psychiatry

*“What a terrible thing to have lost one’s mind. Or not to have a mind at all.  
How true that is.”*

—Dan Quayle

- ▶ High-Yield Clinical Vignettes
- ▶ Pathology
- ▶ Pharmacology

## ► PSYCHIATRY—HIGH-YIELD CLINICAL VIGNETTES

■ Person demands only the best and most famous doctor in town.	What is the personality disorder?	Narcissistic personality disorder.
■ Nurse has episodes of hypoglycemia; blood analysis reveals no elevation in C protein.	What is the diagnosis?	Factitious disorder; self-scripted insulin.
■ 55-year-old businessman complains of lack of successful sexual contacts with women and lack of ability to reach a full erection. Two years ago he had a heart attack.	What might be the cause of his problem?	Fear of sudden death during intercourse.
■ 15-year-old girl of normal height and weight for her age has enlarged parotid glands but no other complaints. The mother confides that she found laxatives in the daughter's closet.	What is the diagnosis?	Bulimia.
■ Man on several medications, including antidepressants and antihypertensives, has mydriasis and becomes constipated.	What is the cause of his symptoms?	TCA.
■ Woman on MAO inhibitor has hypertensive crisis after a meal.	What did she ingest?	Tyramine (wine or cheese).

<b>Infant deprivation effects</b>	<p>Long-term deprivation of affection results in:</p> <ol style="list-style-type: none"> <li>1. ↓ muscle tone</li> <li>2. Poor language skills</li> <li>3. Poor socialization skills</li> <li>4. Lack of basic trust</li> <li>5. Anaclitic depression</li> <li>6. Weight loss</li> <li>7. Physical illness</li> </ol> <p>Severe deprivation can result in infant death.</p>	<p>The 4 W's: Weak, Wordless, Wanting (socially), Wary.</p> <p>Deprivation for &gt; 6 months can lead to irreversible changes.</p>
<b>Anaclitic depression</b>	Depression in an infant owing to continued separation from caregiver—can result in failure to thrive. Infant becomes withdrawn and unresponsive.	
<b>Regression in children</b>	Children regress to younger behavior under stress—physical illness, punishment, birth of a new sibling, tiredness. An example is bed-wetting in a previously toilet-trained child when hospitalized.	
<b>Childhood and early-onset disorders</b>	<p><b>Autistic disorder</b>—patients have severe communication problems and difficulty forming relationships. Characterized by repetitive behavior, unusual abilities (savants), and usually below-normal intelligence. Treatment: ↑ communication and social skills.</p> <p><b>Asperger disorder</b>—a milder form of autism involving problems with social relationships and repetitive behavior. Children are of normal intelligence and lack social or cognitive deficits.</p> <p><b>Rett disorder</b>—X-linked disorder seen only in girls (affected males die in utero). Characterized by loss of development and mental retardation appearing at approximately age 4. Stereotyped hand-wringing.</p> <p><b>Attention-deficit hyperactivity disorder (ADHD)</b>—limited attention span and hyperactivity. Children are emotionally labile, impulsive, and prone to accidents. Normal intelligence. Treatment: methylphenidate (Ritalin).</p> <p><b>Conduct disorder</b>—continued behavior violating social norms. At &gt; 18 years of age, diagnosed as antisocial personality disorder.</p> <p><b>Oppositional defiant disorder</b>—child is noncompliant in the absence of criminality.</p> <p><b>Tourette's syndrome</b>—motor/vocal tics and involuntary profanity. Onset &lt; 18 years. Treatment: haloperidol.</p> <p><b>Separation anxiety disorder</b>—fear of loss of attachment figure leading to factitious physical complaints to avoid going to school. Common onset age 7–8.</p>	
<b>Child abuse</b>	<p><b>Physical abuse</b></p> <p>Evidence: Healed fractures on x-ray, cigarette burns, subdural hematomas, multiple bruises, retinal hemorrhage or detachment</p> <p>Abuser: Usually female and the 1° caregiver</p> <p>Epidemiology: ~3000 deaths/year in the United States</p>	<p><b>Sexual abuse</b></p> <p>Genital/anal trauma, STDs, UTIs</p> <p>Known to victim, usually male</p> <p>Peak incidence 9–12 years of age</p>

<b>Neurotransmitter changes with disease</b>	<p>Anxiety—↑ NE, ↓ GABA, ↓ serotonin (5-HT).          Depression—↓ NE and ↓ serotonin (5-HT).          Alzheimer's dementia—↓ ACh.          Huntington's disease—↓ GABA, ↓ ACh.          Schizophrenia—↑ dopamine.          Parkinson's disease—↓ dopamine.</p>	
<b>Orientation</b>	<p>Is the patient aware of him- or herself as a person?          Does the patient know his or her own name?          Anosognosia—unaware that one is ill.          Autotopagnosia—unable to locate one's own body parts.          Depersonalization—body seems unreal or dissociated.</p>	<p>Order of loss: 1st—time;          2nd—place; last—person.</p>
<b>Amnesia types</b>	<p><i>Anterograde</i> amnesia—inability to remember things that occurred after a CNS insult (no new memory).          Korsakoff's amnesia—classic anterograde amnesia that is caused by thiamine deficiency (bilateral destruction of the mammillary bodies), is seen in alcoholics, and associated with confabulations.  <i>Retrograde</i> amnesia—inability to remember things that occurred before a CNS insult.</p>	
<b>Delirium</b>	<p>Waxing and waning level of consciousness; rapid ↓ in attention span and level of arousal—disorganized thinking, hallucinations, illusions, misperceptions, disturbance in sleep-wake cycle, cognitive dysfunction.          Often due to substance use/abuse or medical illness.          Abnormal EEG.</p>	<p><b>DeliriUM</b> = changes in <b>sensoriUM</b>.          Most common psychiatric illness on medical and surgical floors. Often reversible.          Check for drugs with anticholinergic effects.</p>
<b>Dementia</b>	<p>Gradual ↓ in cognition—memory deficits, aphasia, apraxia, agnosia, loss of abstract thought, behavioral/personality changes, impaired judgment. Patient is alert; no change in level of consciousness.          More often gradual onset.</p>	<p><b>DeMEM</b>tia characterized by <b>MEM</b>ory loss. Commonly irreversible.          In elderly patients, depression may present like dementia.          Normal EEG.</p>
<b>Hallucination vs. illusion vs. delusion vs. loose association</b>	<p>Hallucinations are perceptions in the absence of external stimuli.          Illusions are misinterpretations of actual external stimuli.          Delusions are false beliefs not shared with other members of culture/subculture that are firmly maintained in spite of obvious proof to the contrary.          Loose associations are disorders in the form of thought (the way ideas are tied together).</p>	

<b>Hallucination types</b>	<p>Visual and auditory hallucinations are common in schizophrenia.</p> <p>Olfactory hallucination often occurs as an aura of a psychomotor epilepsy.</p> <p>Gustatory hallucination is rare.</p> <p>Tactile hallucination (e.g., formication—the sensation of ants crawling on one's skin) is common in DTs. Also seen in cocaine abusers (“cocaine bugs”).</p> <p>Hypna<b>GO</b>ic hallucination occurs while <b>GO</b>ing to sleep.</p> <p>Hypnopompic hallucination occurs while waking from sleep.</p>	
<b>Schizophrenia</b>	<p>Periods of psychosis and disturbed behavior with a decline in functioning lasting &gt; 6 months (1–6 months—schizophreniform disorder; &lt; 1 month—brief psychotic disorder, usually stress related).</p> <p>Diagnosis requires 2 or more of the following (1–4 are “positive symptoms”):</p> <ol style="list-style-type: none"> <li>1. Delusions</li> <li>2. Hallucinations—often auditory</li> <li>3. Disorganized thought (loose associations)</li> <li>4. Disorganized or catatonic behavior</li> <li>5. “Negative symptoms”—flat affect, social withdrawal, lack of motivation, lack of speech or thought</li> </ol> <p>Genetic factors outweigh environmental factors in the etiology of schizophrenia.</p> <p>Lifetime prevalence—1.5% (males = females, blacks = whites). Presents earlier in men.</p>	<p>5 subtypes:</p> <ol style="list-style-type: none"> <li>1. Disorganized</li> <li>2. Catatonic</li> <li>3. Paranoid</li> <li>4. Undifferentiated</li> <li>5. Residual</li> </ol> <p>Schizoaffective disorder—a combination of schizophrenia and a mood disorder.</p>
<b>Hypomanic episode</b>	<p>Like manic episode except mood disturbance not severe enough to cause marked impairment in social and/or occupational functioning or to necessitate hospitalization; there are no psychotic features.</p>	
<b>Manic episode</b>	<p>Distinct period of abnormally and persistently elevated, expansive, or irritable mood lasting at least 1 week.</p> <p>During mood disturbance, 3 or more of the following are present:</p> <ol style="list-style-type: none"> <li>1. Distractibility</li> <li>2. Irresponsibility—seeks pleasure without regard to consequences (hedonistic)</li> <li>3. Grandiosity—inflated self-esteem</li> <li>4. Flight of ideas—racing thoughts</li> <li>5. ↑ in goal-directed Activity/psychomotor Agitation</li> <li>6. ↓ need for Sleep</li> <li>7. Talkativeness or pressured speech</li> </ol>	<b>DIG FAST.</b>



<b>Bipolar disorder</b>	6 separate criteria sets exist for bipolar disorders with combinations of manic (bipolar I), hypomanic (bipolar II), and depressed episodes. 1 manic or hypomanic episode defines bipolar disorder. Lithium is drug of choice. <b>Cyclothymic disorder</b> is a milder form lasting at least 2 years.
<b>Major depressive episode</b>	Characterized by at least 5 of the following for 2 weeks, including either depressed mood or anhedonia: <ol style="list-style-type: none"> <li>1. Sleep disturbance</li> <li>2. Loss of Interest (anhedonia)</li> <li>3. Guilt or feelings of worthlessness</li> <li>4. Loss of Energy</li> <li>5. Loss of Concentration</li> <li>6. Change in Appetite/weight</li> <li>7. Psychomotor retardation or agitation</li> <li>8. Suicidal ideations</li> <li>9. Depressed mood</li> </ol> <p>Lifetime prevalence of major depressive episode—5–12% male, 10–25% female. Major depressive disorder, recurrent—requires 2 or more episodes with a symptom-free interval of 2 months. <b>Dysthymia</b> is a milder form of depression lasting at least 2 years.</p>
<b>Risk factors for suicide completion</b>	Sex (male), Age (teenager or elderly), Depression, Previous attempt, Ethanol or drug use, loss of Rational thinking, Sickness (medical illness, 3 or more prescription medications), Organized plan, No spouse (divorced, widowed, or single, especially if childless), Social support lacking. Women try more often; men succeed more often.
<b>Sleep patterns of depressed patients</b>	Patients with depression typically have the following changes in their sleep stages: <ol style="list-style-type: none"> <li>1. ↓ slow-wave sleep</li> <li>2. ↓ REM latency</li> <li>3. ↑ REM early in sleep cycle</li> <li>4. ↑ total REM sleep</li> <li>5. Repeated nighttime awakenings</li> <li>6. Early-morning awakening (important screening question)</li> </ol>
<b>Electroconvulsive therapy</b>	Treatment option for major depressive disorder refractory to other treatment. Produces a painless seizure. Major adverse effects of ECT are disorientation, anterograde and retrograde amnesia.

<b>Panic disorder</b>	<p>Recurrent periods of intense fear and discomfort peaking in 10 minutes with 4 of the following: Palpitations, Paresthesias, Abdominal distress, Nausea, Intense fear of dying or losing control, lightheadedness, Chest pain, Chills, Choking, disconnectedness, Sweating, Shaking, Shortness of breath.</p> <p>Panic is described in context of occurrence (e.g., panic disorder with agoraphobia). High incidence during Step 1 exam.</p>	<b>PANICS.</b>
<b>Specific phobia</b>	<p>Fear that is excessive or unreasonable and interferes with normal routine. <b>Cued</b> by presence or anticipation of a specific object or situation. Person recognizes fear is excessive (insight), yet exposure provokes an anxiety response. Can treat with systematic desensitization. Examples include:</p> <ol style="list-style-type: none"> <li>1. Gamophobia (<i>gam</i> = gamete)—fear of marriage</li> <li>2. Algophobia (<i>alg</i> = pain)—fear of pain</li> <li>3. Acrophobia (<i>acro</i> = height)—fear of heights</li> <li>4. Agoraphobia (<i>agora</i> = open market)—fear of open places</li> </ol>	
<b>Post-traumatic stress disorder</b>	<p>Persistent reexperiencing of a previous traumatic event in the life of the patient as nightmares or flashbacks. Response involves intense fear, helplessness, or horror. Leads to avoidance of stimuli associated with the trauma and persistently increased arousal. Disturbance lasts &gt; 1 month and causes distress or social/occupational impairment. PTSD often follows acute stress disorder, which lasts up to 2–4 weeks.</p>	
<b>Other anxiety disorders</b>	<p><b>Adjustment disorder</b>—emotional symptoms (anxiety, depression) causing impairment following an identifiable psychosocial stressor (e.g., divorce, moving) and lasting &lt; 6 months.</p> <p><b>Generalized anxiety disorder</b>—uncontrollable anxiety for at least 6 months that is unrelated to a specific person, situation, or event. Sleep disturbance, fatigue, and difficulty concentrating are common.</p>	
<b>Malingering</b>	<p>Patient consciously fakes or claims to have a disorder in order to attain a specific gain (e.g., avoiding work, obtaining drugs).</p>	
<b>Factitious disorder</b>	<p>Consciously creates symptoms in order to assume “sick role” and to get medical attention. <b>Munchausen’s syndrome</b> is manifested by a chronic history of multiple hospital admissions and willingness to receive invasive procedures. <b>Munchausen’s syndrome by proxy</b> is seen when illness in a child is caused by the parent. Motivation is unconscious. Is a form of child abuse and must be reported.</p>	

**Somatoform disorders**

Both illness production and motivation are unconscious drives. More common in women.  
Several types:

1. **Conversion**—motor or sensory symptoms (e.g., paralysis, pseudoseizure) that suggest neurologic or physical disorder, but tests and physical exam are negative; often follows an acute stressor; patient may be unconcerned about symptoms
2. **Somatoform pain disorder**—prolonged pain that is not explained completely by illness
3. **Hypochondriasis**—preoccupation with and fear of having a serious illness in spite of medical reassurance
4. **Somatization disorder**—variety of complaints in multiple organ systems with no identifiable underlying physical findings
5. **Body dysmorphic disorder**—preoccupation with minor or imagined physical flaws; patients often seek cosmetic surgery
6. **Pseudocyesis**—false belief of being pregnant associated with objective physical signs of pregnancy

**Gain: 1°, 2°, 3°**

1° gain—what the symptom does for the patient's internal psychic economy.  
2° gain—what the symptom gets the patient (sympathy, attention).  
3° gain—what the caretaker gets (like an MD on an interesting case).

**Personality**

Personality trait—an enduring pattern of perceiving, relating to, and thinking about the environment and oneself that is exhibited in a wide range of important social and personal contexts.  
Personality disorder—when these patterns become inflexible and maladaptive, causing impairment in social or occupational functioning or subjective distress; person is usually not aware of problem. Disordered patterns must be stable by early adulthood; not usually diagnosed in children.

**Cluster A personality disorders**

Odd or eccentric; cannot develop meaningful social relationships. No psychosis; genetic association with schizophrenia. **“Weird.”**

Types:

1. **Paranoid**—distrust and suspiciousness; projection is main defense mechanism
2. **Schizoid**—voluntary social withdrawal, limited emotional expression, content with social isolation, unlike avoidant
3. **Schizotypal**—interpersonal awkwardness, odd beliefs or magical thinking, eccentric appearance

<b>Cluster B personality disorders</b>	<p>Dramatic, emotional, or erratic; genetic association with mood disorders and substance abuse.</p> <p>Types:</p> <ol style="list-style-type: none"> <li>1. Antisocial—disregard for and violation of rights of others, criminality; males &gt; females; conduct disorder if &lt; 18 years</li> <li>2. Borderline—unstable mood and interpersonal relationships, impulsiveness, sense of emptiness; females &gt; males</li> <li>3. Histrionic—excessive emotionality, attention seeking, sexually provocative</li> <li>4. Narcissistic—grandiosity, sense of entitlement; may react to criticism with rage; may demand “top” physician/best health care</li> </ol>	“Wild.”
<b>Cluster C personality disorders</b>	<p>Anxious or fearful; genetic association with anxiety disorders.</p> <p>Types:</p> <ol style="list-style-type: none"> <li>1. Avoidant—sensitive to rejection, socially inhibited, timid, feelings of inadequacy</li> <li>2. Obsessive-compulsive—preoccupation with order, perfectionism, and control</li> <li>3. Dependent—submissive and clinging, excessive need to be taken care of, low self-confidence</li> </ol>	“Worried.”
<b>Eating disorders</b>	<p><b>Anorexia nervosa</b>—abnormal eating habits (excessive dieting), body image distortion, and ↑ exercise. Severe weight loss, amenorrhea, anemia, and electrolyte disturbances can follow. Seen primarily in adolescent girls. Commonly coexists with depression.</p> <p><b>Bulimia nervosa</b>—binge eating followed by self-induced vomiting or use of laxatives. Body weight is normal. Parotitis, enamel erosion, electrolyte disturbances, alkalosis, dorsal hand calluses from inducing vomiting.</p>	
<b>Substance dependence</b>	<p>Maladaptive pattern of substance use defined as 3 or more of the following signs in 1 year:</p> <ol style="list-style-type: none"> <li>1. Tolerance—need more to achieve same effect.</li> <li>2. Withdrawal</li> <li>3. Substance taken in larger amounts or over longer time than desired</li> <li>4. Persistent desire or attempts to cut down</li> <li>5. Significant energy spent obtaining, using, or recovering from substance</li> <li>6. Important social, occupational, or recreational activities reduced because of substance use</li> <li>7. Continued use in spite of knowing the problems that it causes</li> </ol>	
<b>Substance abuse</b>	<p>Maladaptive pattern leading to clinically significant impairment or distress. Substance dependence plus 1 or more of the following in 1 year:</p> <ol style="list-style-type: none"> <li>1. Recurrent use resulting in failure to fulfill major obligations at work, school, or home</li> <li>2. Recurrent use in physically hazardous situations</li> <li>3. Recurrent substance-related legal problems</li> <li>4. Continued use in spite of persistent problems caused by use</li> </ol>	

**Signs and symptoms of substance abuse**

Drug	Intoxication	Withdrawal
Alcohol	Disinhibition, emotional lability, slurred speech, ataxia, coma, blackouts. Serum $\gamma$ -glutamyltransferase (GGT)—sensitive indicator of alcohol use.	Tremor, tachycardia, hypertension, malaise, nausea, seizures, delirium tremens (DTs), tremulousness, agitation, hallucinations
Opioids	CNS depression, nausea and vomiting, constipation, pupillary constriction (pinpoint pupils), seizures (overdose is life-threatening).	Anxiety, insomnia, anorexia, sweating, dilated pupils, piloerection (“cold turkey”), fever, rhinorrhea, nausea, stomach cramps, diarrhea (“flulike” symptoms), yawning
Amphetamines	Psychomotor agitation, impaired judgment, pupillary dilation, hypertension, tachycardia, euphoria, prolonged wakefulness and attention, cardiac arrhythmias, delusions, hallucinations, fever.	Post-use “crash,” including depression, lethargy, headache, stomach cramps, hunger, hypersomnolence
Cocaine	Euphoria, psychomotor agitation, impaired judgment, tachycardia, pupillary dilation, hypertension, hallucinations (including tactile), paranoid ideations, angina, sudden cardiac death.	Post-use “crash,” including severe depression and suicidality, hypersomnolence, fatigue, malaise, severe psychological craving
PCP	Belligerence, impulsiveness, fever, psychomotor agitation, vertical and horizontal nystagmus, tachycardia, ataxia, homicidality, psychosis, delirium.	Recurrence of intoxication symptoms due to reabsorption in GI tract; sudden onset of severe, random, homicidal violence
LSD	Marked anxiety or depression, delusions, visual hallucinations, flashbacks, pupil dilation.	
Marijuana	Euphoria, anxiety, paranoid delusions, perception of slowed time, impaired judgment, social withdrawal, ↑ appetite, dry mouth, hallucinations.	
Barbiturates	Low safety margin, respiratory depression.	Anxiety, seizures, delirium, life-threatening cardiovascular collapse
Benzodiazepines	Greater safety margin. Amnesia, ataxia, somnolence, minor respiratory depression. Addictive effects with alcohol.	Rebound anxiety, seizures, tremor, insomnia
Caffeine	Restlessness, insomnia, increased diuresis, muscle twitching, cardiac arrhythmias.	Headache, lethargy, depression, weight gain
Nicotine	Restlessness, insomnia, anxiety, arrhythmias.	Irritability, headache, anxiety, weight gain, craving

<b>Heroin addiction</b>	Approximately 500,000 U.S. addicts. Look for track marks (needle sticks in veins). Users at risk for hepatitis, abscesses, overdose, hemorrhoids, AIDS, and right-sided endocarditis.	Naloxone and naltrexone competitively inhibit opioids. Methadone (long-acting oral opiate) for heroin detoxification or long-term maintenance.
<b>Alcoholism</b>	<p>Physiologic tolerance and dependence with symptoms of withdrawal (tremor, tachycardia, hypertension, malaise, nausea, delirium tremens) when intake is interrupted. Continued drinking despite medical and social contraindications and life disruptions.</p> <p>Treatment: disulfiram to condition the patient to abstain from alcohol use. Supportive treatment of other systemic manifestations. Alcoholics Anonymous and other peer support groups are helpful in sustaining abstinence.</p> <div><p>Ethanol</p><div><div>Interpolates into membranes</div><div>Increased membrane fluidity</div><div>Toxic effects, particularly in the brain</div></div><div><div>Alcohol dehydrogenase</div><div>MEOS</div><div>Acetaldehyde</div><div><div>Forms adducts with proteins and nucleic acids</div><div>Converted to acetate</div><div>Converted to acetyl-CoA</div><div>Increased fatty acid synthesis</div><div>Fatty liver</div></div></div><div><div>Increased NADH/NAD:</div><div>Increases lactate/pyruvate</div><div>Inhibits gluconeogenesis</div><div>Inhibits fatty acid oxidation</div><div>Inhibits glycerophosphate dehydrogenase, leading to elevated glycerophosphate</div></div></div>	
<b>Delirium tremens</b>	<p>Life-threatening alcohol withdrawal syndrome that peaks 2–5 days after last drink. In order of appearance—autonomic system hyperactivity (tachycardia, tremors, anxiety), psychotic symptoms (hallucinations, delusions), confusion.</p> <p>Treat with benzodiazepines.</p>	

► **PSYCHIATRY—PATHOLOGY** (*continued*)**Complications of alcoholism**

Alcoholic cirrhosis	Micronodular cirrhosis with jaundice, hypoalbuminemia, coagulation factor deficiencies, and portal hypertension, leading to peripheral edema and ascites, encephalopathy, neurologic manifestations (e.g., asterixis, flapping tremor of the hands), and esophageal varices.
Wernicke-Korsakoff syndrome	Caused by vitamin B <sub>1</sub> (thiamine) deficiency; common in malnourished alcoholics. Triad of confusion, ophthalmoplegia, and ataxia (Wernicke's encephalopathy). May progress to memory loss, confabulation, personality change (Korsakoff's psychosis; irreversible). Associated with periventricular hemorrhage/necrosis, especially in mammillary bodies. Treatment: IV vitamin B <sub>1</sub> (thiamine).
Mallory-Weiss syndrome	Longitudinal lacerations at the gastroesophageal junction caused by excessive vomiting. Associated with pain in contrast to esophageal varices.
Other	Hepatitis, pancreatitis, peripheral neuropathy, testicular atrophy, hyperestrinism.

► **PSYCHIATRY—PHARMACOLOGY****Treatment for selected psychiatric conditions**

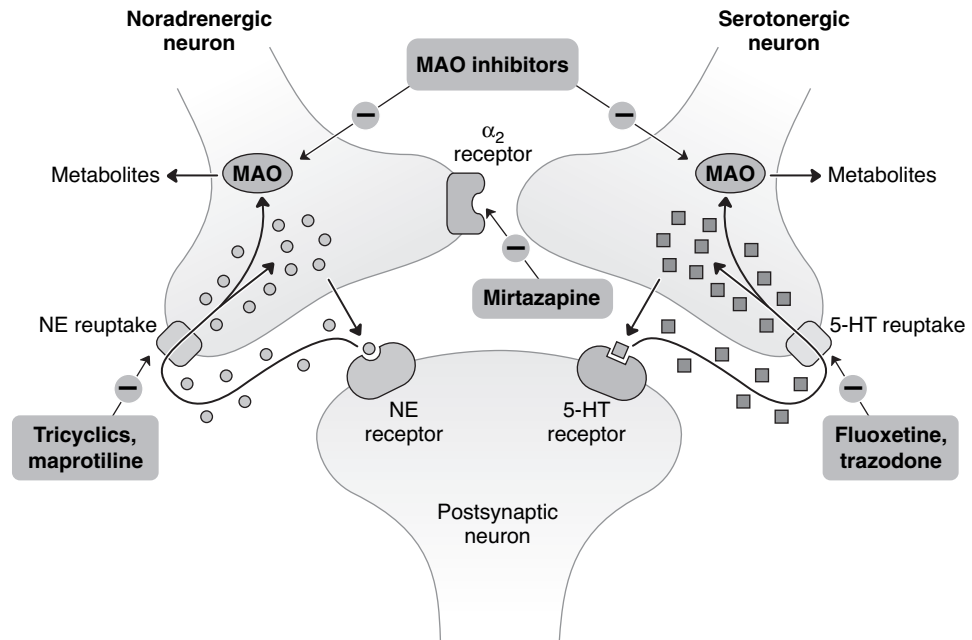
Psychiatric condition	Drug
Alcohol withdraw	Benzodiazepines
Anorexia/bulimia	SSRIs
Anxiety	Barbiturates
	Benzodiazepines
	Buspirone
	MAO inhibitors
Atypical depression	<b>MAO inhibitors</b>
Bipolar disorder	Mood stabilizers:
	Lithium
	Valproic acid
	Carbamazepines
Depression	SSRIs
	TCAs
Depression with insomnia	Trazodone
	Mirtazapine
Obsessive/compulsive disorder	SSRIs
Panic disorder	TCAs
	Buspirone
Schizophrenia	Antipsychotics

<b>Antipsychotics (neuroleptics)</b>	Thioridazine, haloperidol, fluphenazine, chlorpromazine.	
Mechanism	Most antipsychotics block dopamine <b>D<sub>2</sub></b> receptors (excess dopamine effects connected with schizophrenia).	Evolution of EPS side effects: 4 h acute dystonia 4 d akinesia
Clinical use	Schizophrenia, psychosis, acute mania, Tourette syndrome	4 wk akathisia 4 mo tardive dyskinesia (often irreversible)
Toxicity	Extrapyramidal system (EPS) side effects, endocrine side effects (e.g., dopamine receptor antagonism → hyperprolactinemia → gynecomastia), and side effects arising from blocking muscarinic (dry mouth, constipation), $\alpha$ (hypotension), and histamine (sedation) receptors. <b>Neuroleptic malignant syndrome</b> —rigidity, myoglobinuria, autonomic instability, hyperpyrexia (treat with dantrolene and dopamine agonists). <b>Tardive dyskinesia</b> —stereotypic oral-facial movements probably due to dopamine receptor sensitization; results of long-term antipsychotic use.	
<b>Atypical antipsychotics</b>	Clozapine, olanzapine, risperidone.	
Mechanism	Block 5-HT <sub>2</sub> and dopamine receptors.	It's not <b>atypical</b> for old closets to <b>RISPER</b> .
Clinical use	Treatment of schizophrenia; useful for positive and negative symptoms. <b>Olanzapine</b> is also used for OCD, anxiety disorder, depression, mania, Tourette syndrome.	
Toxicity	Fewer extrapyramidal and anticholinergic side effects than other antipsychotics. <b>Clozapine</b> may cause agranulocytosis (requires weekly WBC monitoring).	
<b>Lithium</b>		
Mechanism	Not established; possibly related to inhibition of phosphoinositol cascade.	<b>LMNOP:</b> Lithium side effects—
Clinical use	Mood stabilizer for bipolar affective disorder; blocks relapse and acute manic events.	<b>M</b> ovement (tremor) <b>N</b> ephrogenic diabetes insipidus
Toxicity	Tremor, hypothyroidism, polyuria (ADH antagonist causing nephrogenic diabetes insipidus), teratogenesis. Narrow therapeutic window requiring close monitoring of serum levels.	<b>HypO</b> thyroidism <b>P</b> regnancy problems
<b>Buspirone</b>		
Mechanism	Stimulates 5-HT <sub>1A</sub> receptors	
Clinical use	Anxiolysis for generalized anxiety disorder. Does not cause sedation or addiction. Does not interact with alcohol.	



## Antidepressants

1. SSRIs
2. Tricyclic antidepressants
3. Heterocyclic antidepressants
4. MAOIs



(Adapted, with permission, from Katzung BG, Trevor AJ. *USMLE Road Map: Pharmacology*, 1st ed. New York: McGraw-Hill, 2003:80.)

<b>SSRIs</b>	Fluoxetine, sertraline, paroxetine, citalopram.	
Mechanism	Serotonin-specific reuptake inhibitors.	
Clinical use	Endogenous depression, OCD.	It normally takes 2–3 weeks
Toxicity	Fewer than TCAs. GI distress, sexual dysfunction (anorgasmia). “Serotonin syndrome” with MAO inhibitors—hyperthermia, muscle rigidity, cardiovascular collapse.	for antidepressants to have an effect.

<b>Tricyclic antidepressants</b>	Imipramine, amitriptyline, desipramine, nortriptyline, clomipramine, doxepin.
Mechanism	Block reuptake of NE and serotonin.
Clinical use	Major depression, bedwetting (imipramine), OCD (clomipramine).
Side effects	Sedation, $\alpha$ -blocking effects, atropine-like (anticholinergic) side effects (tachycardia, urinary retention). 3° TCAs (amitriptyline) have more anticholinergic effects than do 2° TCAs (nortriptyline). Desipramine is the least sedating.
Toxicity	<b>Tri-C’s</b> : Convulsions, Coma, Cardiotoxicity (arrhythmias); also respiratory depression, hyperpyrexia. Confusion and hallucinations in elderly due to anticholinergic side effects (use nortriptyline).

**Heterocyclic antidepressants**

<b>Bupropion</b>	Also used for smoking cessation. Mechanism not well known. Toxicity: stimulant effects (tachycardia, insomnia), headache, seizure in bulimic patients. Does not cause sexual side effects.	You need <b>BU</b> tane in your <b>VEINs</b> to <b>MUR</b> der for a <b>MAP</b> of Alca <b>TRAZ</b> .
<b>Venlafaxine</b>	Also used in generalized anxiety disorder. Inhibits serotonin, NE, and dopamine reuptake. Toxicity: stimulant effects, sedation, nausea, constipation, ↑ BP.	
<b>Mirtazapine</b>	$\alpha_2$ antagonist (↑ release of NE and serotonin) and potent 5-HT <sub>2</sub> and 5-HT <sub>3</sub> receptor antagonist. Toxicity: sedation, ↑ appetite, weight gain, dry mouth.	
<b>Maprotiline</b>	Blocks NE reuptake. Toxicity: sedation, orthostatic hypotension.	
<b>Trazodone</b>	Primarily inhibit serotonin reuptake. Toxicity: sedation, nausea, priapism, postural hypotension.	

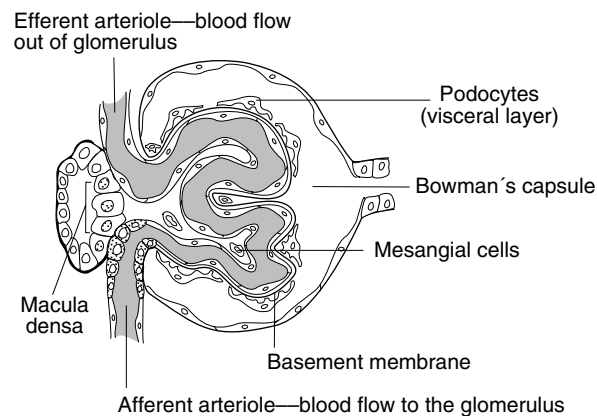
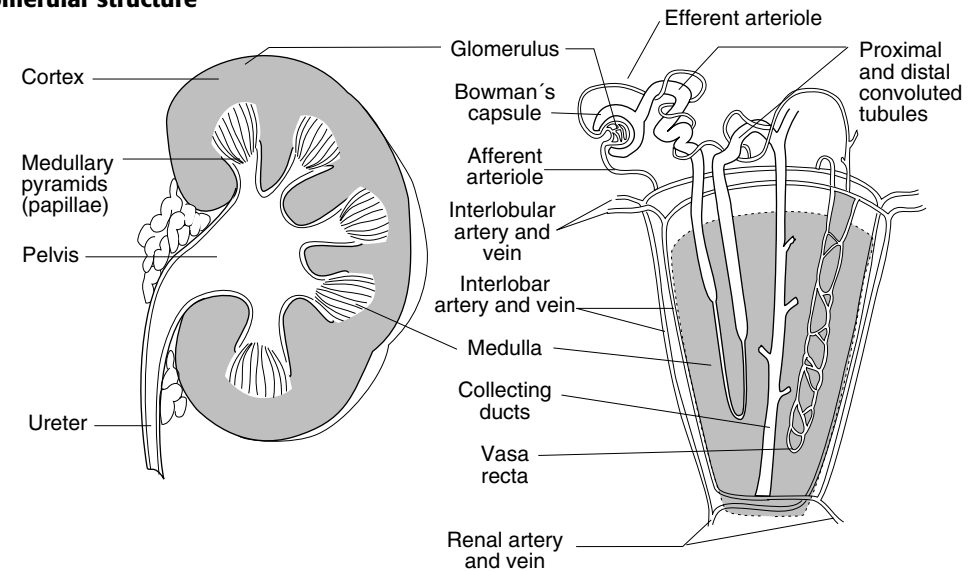
**Monoamine oxidase (MAO) inhibitors**

Mechanism	Nonselective MAO inhibition → ↑ levels of amine neurotransmitters.
Clinical use	Atypical depression (i.e., with psychotic or phobic features), anxiety, hypochondriasis.
Toxicity	Hypertensive crisis with tyramine ingestion (in many foods) and meperidine; CNS stimulation. Contraindication with SSRIs or $\beta$ -agonists (to prevent serotonin syndrome).

## RENAL—HIGH-YIELD CLINICAL VIGNETTES

- |                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                               |                                                                                                                                                                                                                       |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"><li>■ 3-year-old boy presents with facial edema, malaise, and proteinuria.</li><li>■ Woman presents with UTI positive for <i>Proteus vulgaris</i>.</li><li>■ Patient describes a 2-year history of acetaminophen use.</li><li>■ X-ray film shows massively enlarged kidneys bilaterally.</li><li>■ Patient taking enalapril complains of constant coughing.</li></ul> | <p>What is the appropriate treatment?</p> <p>What type of kidney stones is she at risk for?</p> <p>What is she at risk for?</p> <p>What is the diagnosis?</p> <p>What is an appropriate alternative drug?</p> | <p>Steroids for minimal change disease.</p> <p>Ammonium magnesium phosphate (struvite).</p> <p>Renal papillary necrosis.</p> <p>Adult polycystic kidney disease.</p> <p>Losartan—angiotensin II receptor blocker.</p> |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

## Kidney anatomy and glomerular structure



The left kidney is taken during transplantation because it has a longer renal vein.

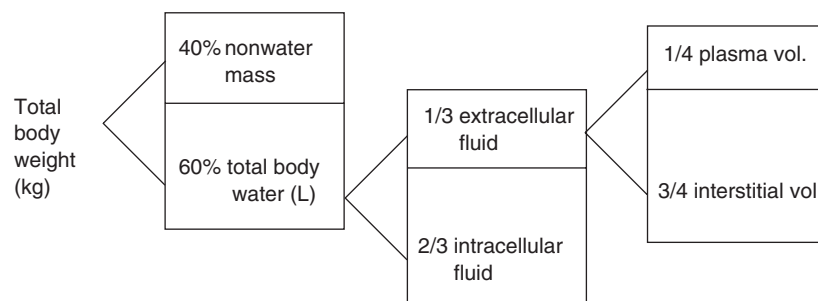
(Adapted, with permission, from McPhee S et al. *Pathophysiology of Disease: An Introduction to Clinical Medicine*, 3rd ed. New York: McGraw-Hill, 2000:384.)

### Ureters: course

Ureters pass **under** uterine artery and **under** ductus deferens (retroperitoneal).

Water (ureters) **under** the bridge (artery, ductus deferens).

## Fluid compartments



ECF:  $\uparrow \text{NaCl}$ ,  $\downarrow \text{K}^+$   
 ICF:  $\uparrow \text{K}^+$ ,  $\downarrow \text{NaCl}$   
 $\text{TBW} - \text{ECF} = \text{ICF}$ .  
 $\text{ECF} - \text{PV} = \text{interstitial volume}$ .  
 60-40-20 rule (% of body weight):  
 60% total body water  
 40% ICF  
 20% ECF  
 Plasma volume measured by  
 radiolabeled albumin.  
 Extracellular volume measured  
 by inulin.  
 Osmolarity = 290 mOsm

### Renal clearance

$C_x = U_x V / P_x$  = volume of plasma from which the substance is completely cleared per unit time.  
 If  $C_x < \text{GFR}$ , then there is net tubular reabsorption of X.  
 If  $C_x > \text{GFR}$ , then there is net tubular secretion of X.  
 If  $C_x = \text{GFR}$ , then there is no net secretion or reabsorption.

Be familiar with calculations.  
 $C_x$  = clearance of X.  
 $U_x$  = urine concentration of X.  
 $P_x$  = plasma concentration of X.  
 $V$  = urine flow rate.

### Glomerular filtration barrier

Responsible for filtration of plasma according to size and net charge.  
 Composed of:  
 1. Fenestrated capillary endothelium (size barrier)  
 2. Fused basement membrane with heparan sulfate (negative charge barrier)  
 3. Epithelial layer consisting of podocyte foot processes

The charge barrier is lost in **nephrotic syndrome**, resulting in albuminuria, hypoproteinemia, generalized edema, and hyperlipidemia.

### Glomerular filtration rate

Inulin can be used to calculate GFR because it is freely filtered and is neither reabsorbed nor secreted.  

$$\text{GFR} = U_{\text{inulin}} \times V / P_{\text{inulin}} = C_{\text{inulin}}$$

$$= K_f [(P_{\text{GC}} - P_{\text{BS}}) - (\pi_{\text{GC}} - \pi_{\text{BS}})]$$
 (GC = glomerular capillary; BS = Bowman's space.)  
 $\pi_{\text{BS}}$  normally equals zero.

Creatinine clearance is an approximate measure of GFR.

### Effective renal plasma flow

ERPF can be estimated using PAH because it is both filtered and actively secreted in the proximal tubule. All PAH entering the kidney is excreted.  

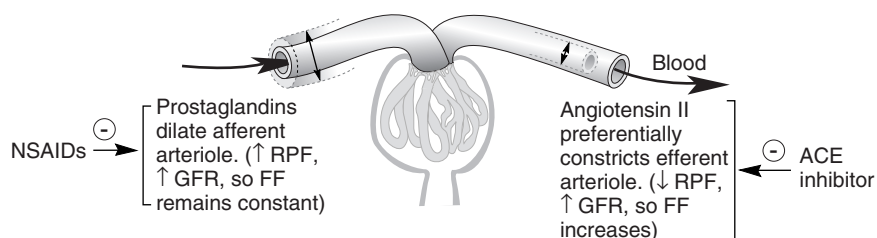
$$\text{ERPF} = U_{\text{PAH}} \times V / P_{\text{PAH}} = C_{\text{PAH}}$$

$$\text{RBF} = \text{RPF} / (1 - \text{Hct})$$
 ERPF underestimates true RPF by ~10%.

**Filtration**

Filtration fraction =  $GFR/RPF$ .

Filtered load =  $GFR \times \text{plasma concentration}$ .

**Changes in renal function**

Effect	RPF	GFR	FF (GFR/RPF)
Afferent arteriole constriction	↓	↓	NC
Efferent arteriole constriction	↓	↑	↑
↑ plasma protein concentration	NC	↓	↓
↓ plasma protein concentration	NC	↑	↑
Constriction of ureter	NC	↓	↓

**Free water clearance**

Given urine flow rate, urine osmolarity, and plasma osmolarity, be able to calculate free water clearance:

$$C_{H_2O} = V - C_{osm}$$

$$V = \text{urine flow rate}; C_{osm} = U_{osm} V / P_{osm}$$

**Glucose clearance**

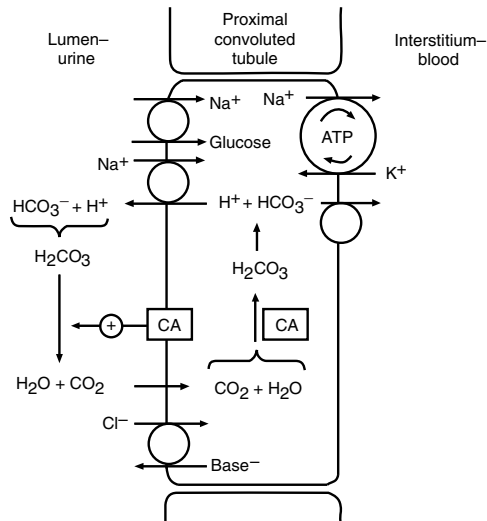
Glucose at a normal plasma level is completely reabsorbed in proximal tubule. At plasma glucose of 200 mg/dL, glucosuria begins (threshold). At 350 mg/dL, transport mechanism is saturated ( $T_m$ ).

Glucosuria is an important clinical clue to diabetes mellitus.

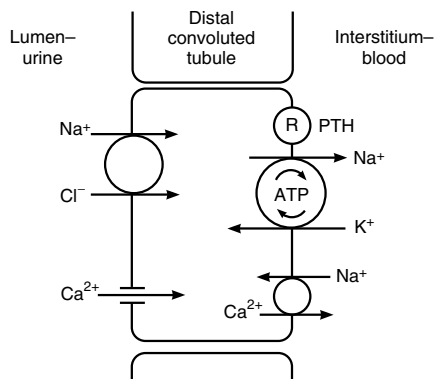
**Amino acid clearance**

Reabsorption by at least 3 distinct carrier systems, with competitive inhibition within each group.  $2^\circ$  active transport occurs in proximal tubule and is saturable.

## Nephron physiology

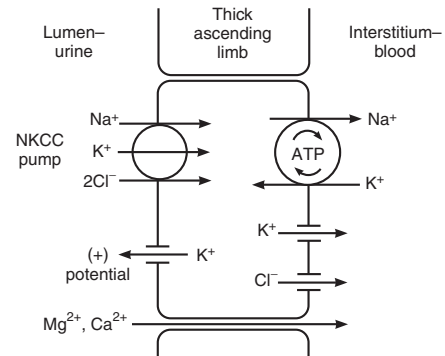


- A. Early proximal convoluted tubule — “workhorse of the nephron.” Reabsorbs **all** of the glucose and amino acids and **most** of the bicarbonate, sodium, and water. Secretes ammonia, which acts as a buffer for secreted  $H^+$ .

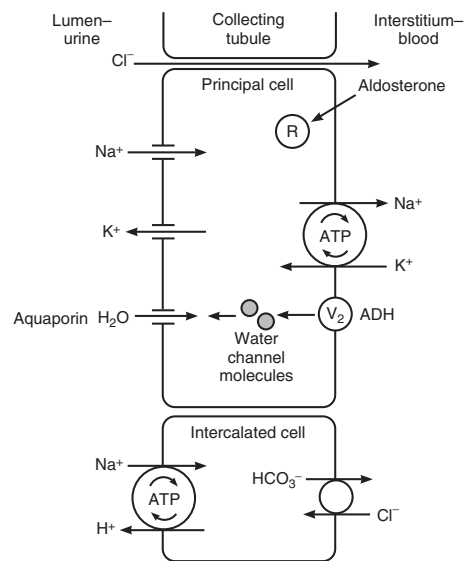


- D. Early distal convoluted tubule — actively reabsorbs  $Na^+$ ,  $Cl^-$ . Reabsorption of  $Ca^{2+}$  is under the control of PTH.

- B. Thin descending loop of Henle — passively reabsorbs water via medullary hypertonicity (impermeable to sodium).

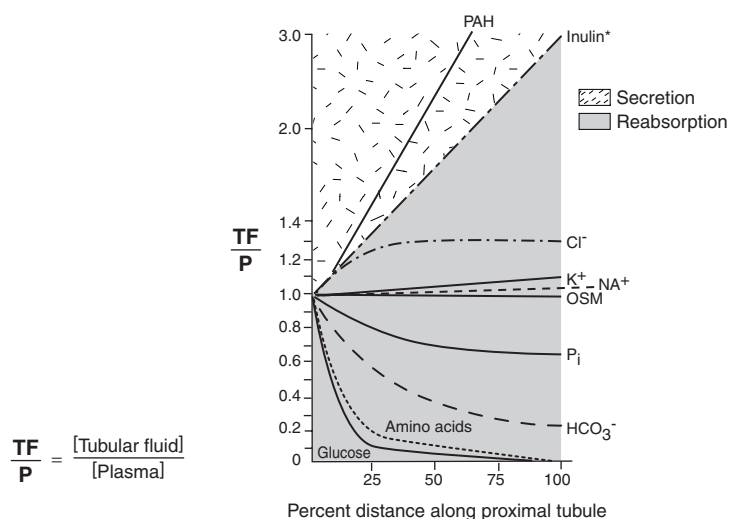


- C. Thick ascending loop of Henle — actively reabsorbs  $Na^+$ ,  $K^+$ , and  $Cl^-$  and indirectly induces the reabsorption of  $Mg^{2+}$  and  $Ca^{2+}$ . Impermeable to  $H_2O$ .



- E. Collecting tubules — reabsorb  $Na^+$  in exchange for secreting  $K^+$  or  $H^+$  (regulated by aldosterone). Reabsorption of water is regulated by ADH (vasopressin). Osmolarity of medulla can reach 1200 mOsm/L  $H_2O$ .

## Relative concentrations along renal tubule

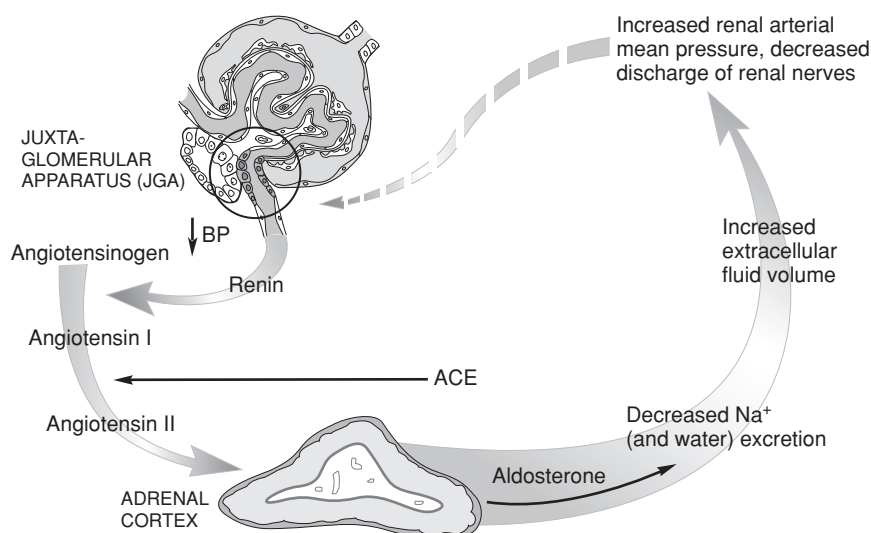


\* Neither secreted nor reabsorbed; concentration increases as water is reabsorbed.

(Adapted, with permission, from Ganong WF. *Review of Medical Physiology*, 22nd ed. New York: McGraw-Hill, 2005.)

## Renin-angiotensin system

- Mechanism** Renin is released by the kidneys upon sensing ↓ BP and cleaves angiotensinogen to angiotensin I. Angiotensin I is then cleaved by angiotensin-converting enzyme (ACE), primarily in the lung capillaries, to angiotensin II.
- Actions of angiotensin II**
1. Potent vasoconstriction
  2. Release of aldosterone from the adrenal cortex
  3. Release of ADH from posterior pituitary
  4. Stimulates hypothalamus → ↑ thirst
- Overall, angiotensin II serves to ↑ intravascular volume and ↑ BP.
- ANP released from atria may act as a “check” on the renin-angiotensin system (e.g., in heart failure). Decreases renin and increases GFR.



(Adapted, with permission, from Ganong WF. *Review of Medical Physiology*, 22nd ed. New York: McGraw-Hill, 2005.)



**Juxtaglomerular apparatus (JGA)**

JGA—JG cells (modified smooth muscle of afferent arteriole) and macula densa ( $\text{Na}^+$  sensor, part of the distal convoluted tubule). JG cells secrete renin (leading to  $\uparrow$  angiotensin II and aldosterone levels) in response to  $\downarrow$  renal blood pressure,  $\downarrow$   $\text{Na}^+$  delivery to distal tubule, and  $\uparrow$  sympathetic tone.

JGA defends glomerular filtration rate via the renin-angiotensin system.

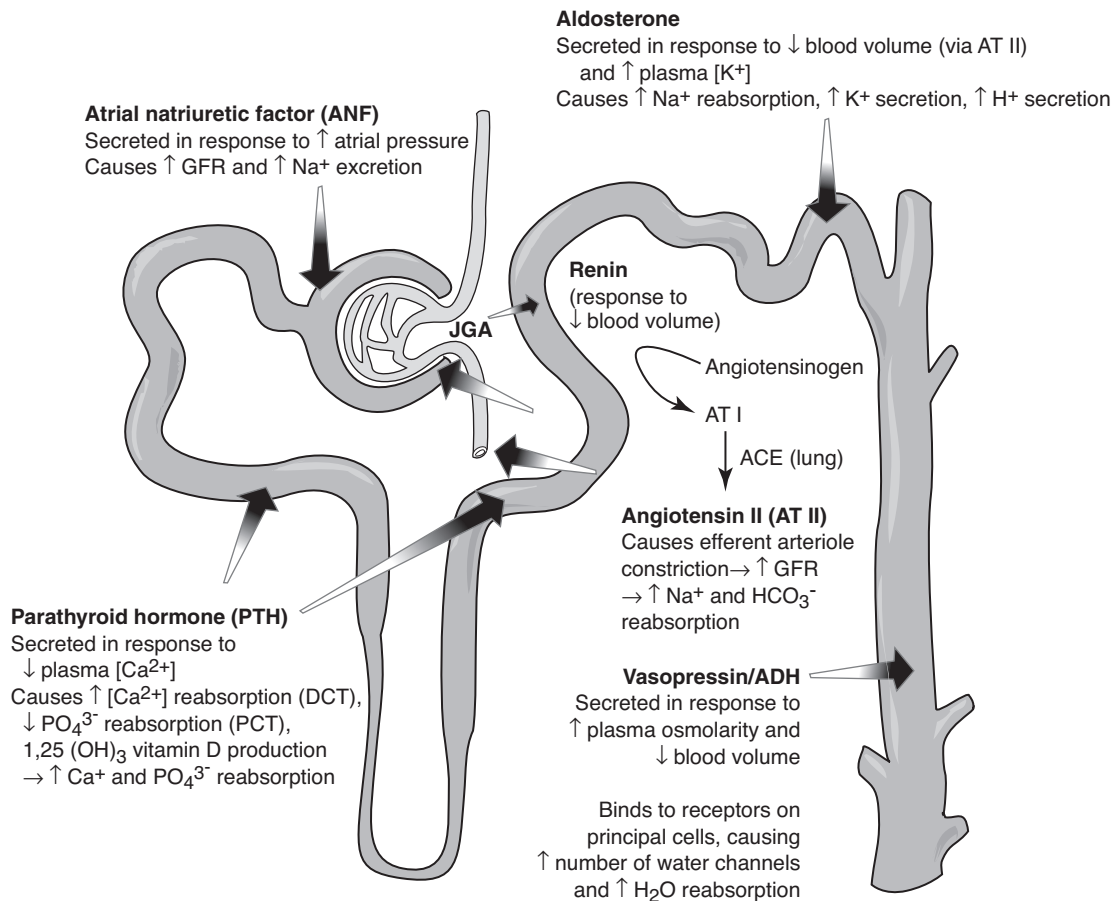
*Juxta* = close by.

**Kidney endocrine functions**

1. Endothelial cells of peritubular capillaries secrete erythropoietin in response to hypoxia
2. Conversion of 25-OH vitamin D to  $1,25\text{-(OH)}_2$  vitamin D by  $1\alpha$ -hydroxylase, which is activated by PTH
3. JG cells secrete renin in response to  $\downarrow$  renal arterial pressure and  $\uparrow$  renal sympathetic discharge ( $\beta_1$  effect)
4. Secretion of prostaglandins that vasodilate the afferent arterioles to  $\uparrow$  GFR

NSAIDs can cause acute renal failure in high vasoconstrictive states by inhibiting the renal production of prostaglandins, which keep the afferent arterioles vasodilated to maintain GFR.

**Hormones acting on kidney**

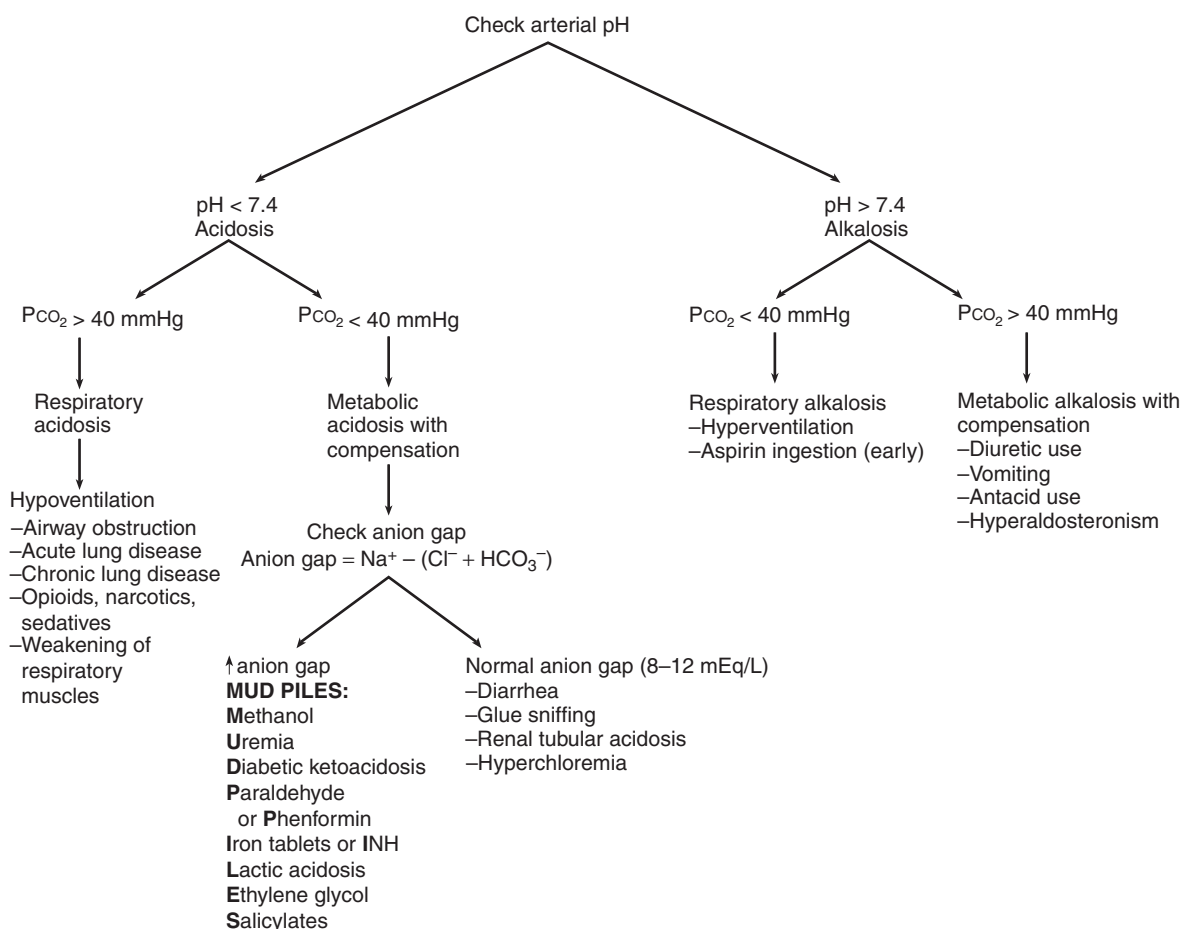


**Acid-base physiology**

	pH	Pco <sub>2</sub>	[HCO <sub>3</sub> <sup>-</sup> ]	Compensatory response
Metabolic acidosis	↓	↓	↓	Hyperventilation
Metabolic alkalosis	↑	↑	↑	Hypoventilation
Respiratory acidosis	↓	↑	↑	↑ Renal [HCO <sub>3</sub> <sup>-</sup> ] reabsorption
Respiratory alkalosis	↑	↓	↓	↓ Renal [HCO <sub>3</sub> <sup>-</sup> ] reabsorption

$$\text{Henderson-Hasselbalch equation: } \text{pH} = \text{pK}_a + \log \frac{[\text{HCO}_3^-]}{0.03 \text{ Pco}_2}$$

Key: ↑ ↓ = primary disturbance; ↓ ↑ = compensatory response.

**Acidosis/alkalosis**

**Acid-base compensations**

Metabolic acidosis  
Metabolic alkalosis  
Respiratory acidosis  
  
Respiratory alkalosis

The following formulas give appropriate compensations for a single disorder. If the formula does not match the actual values, suspect a mixed disorder.

Winter's formula:  $PCO_2 = 1.5 (HCO_3^-) + 8 \pm 2$ .

$PCO_2 \uparrow 0.7$  mmHg for every  $\uparrow 1$  mEq/L  $HCO_3^-$ .

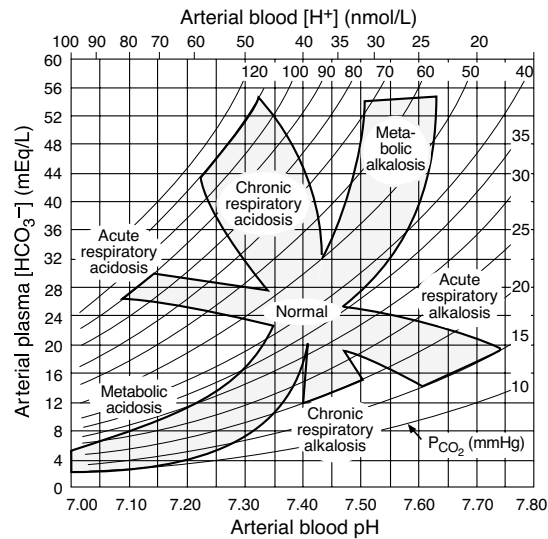
Acute —  $\uparrow 1$  mEq/L  $HCO_3^-$  for every  $\uparrow 10$  mmHg  $PCO_2$ .

Chronic —  $\uparrow 3.5$  mEq/L  $HCO_3^-$  for every  $\uparrow 10$  mmHg  $PCO_2$ .

Acute —  $\downarrow 2$  mEq/L  $HCO_3^-$  for every  $\downarrow 10$  mmHg  $PCO_2$ .

Chronic —  $\downarrow 5$  mEq/L  $HCO_3^-$  for every  $\downarrow 10$  mmHg  $PCO_2$ .

**Acid-base nomogram**



(Adapted, with permission, from Ganong WF. *Review of Medical Physiology*, 22nd ed. New York: McGraw-Hill, 2005:734.)

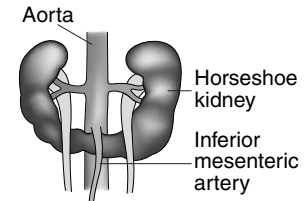
**Potter's syndrome**

Bilateral renal agenesis → oligohydramnios → limb deformities, facial deformities, pulmonary hypoplasia. Caused by malformation of ureteric bud.

Babies with Potter's can't "Pee" in utero.

**Horseshoe kidney**

Inferior poles of both kidneys fuse. As they ascend from pelvis during fetal development, horseshoe kidneys get trapped under inferior mesenteric artery and remain low in the abdomen.

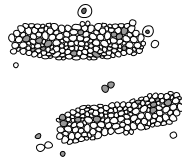


**Casts**

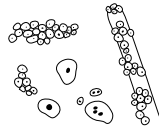
Casts in urine:

RBC casts—glomerular inflammation (nephritic syndromes), ischemia, or malignant hypertension.  
WBC casts—tubulointerstitial disease, acute pyelonephritis, glomerular disorders.  
Granular casts—acute tubular necrosis.  
Waxy casts—advanced renal disease/CRF.  
Hyaline casts—nonspecific.

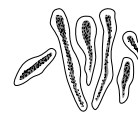
Presence of casts indicates that hematuria/pyuria is of renal origin.  
Bladder cancer → RBCs.  
Acute cystitis → WBCs.



Red blood cell casts



White blood cell casts



Hyaline casts



Granular casts

### Glomerular pathology

**Nephritic syndrome**—hematuria, hypertension, oliguria, azotemia.

1. **Acute poststreptococcal glomerulonephritis**—LM: glomeruli enlarged and hypercellular, neutrophils, “lumpy-bumpy.” EM: subepithelial humps. IF: granular pattern.
2. **Rapidly progressive (crescentic) glomerulonephritis**—LM and IF: crescent-moon shape.
3. **Goodpasture’s syndrome (type II hypersensitivity)**—IF: linear pattern, anti-GBM antibodies.
4. **Membranoproliferative glomerulonephritis**—EM: subendothelial humps, “tram track.”
5. **IgA nephropathy (Berger’s disease)**—IF and EM: mesangial deposits of IgA.
6. **Alport’s syndrome**—split basement membrane.

**Nephrotic syndrome**—massive proteinuria (frothy urine), hypoalbuminemia, peripheral and periorbital edema, hyperlipidemia.

1. **Membranous glomerulonephritis**—LM: diffuse capillary and basement membrane thickening. IF: granular pattern. EM: “spike and dome.”
2. **Minimal change disease (lipoid nephrosis)**—LM: normal glomeruli. EM: foot process effacement (see Color Image 93).
3. **Focal segmental glomerular sclerosis**—LM: segmental sclerosis and hyalinosis.
4. **Diabetic nephropathy**—LM: Kimmelstiel-Wilson “wire loop” lesions, basement membrane thickening (see Color Image 95).
5. **SLE (5 patterns of renal involvement)**—LM: In membranous glomerulonephritis pattern, wire-loop lesion with subepithelial deposits.
6. **Amyloidosis**—IF: Congo red stain, apple green birefringence.

**I** = inflammation.

Most frequently seen in children. Peripheral and periorbital edema. Resolves spontaneously.

Rapid course to renal failure. Number of crescents indicates prognosis.

Hemoptysis, hematuria.

Slowly progresses to renal failure.

Mild disease. Often postinfectious.

Collagen IV mutation. Nerve deafness and ocular disorders.

**O** = prOteinuria.

Most common cause of adult nephrotic syndrome.

Most common cause of childhood nephrotic syndrome. Responds well to steroids.

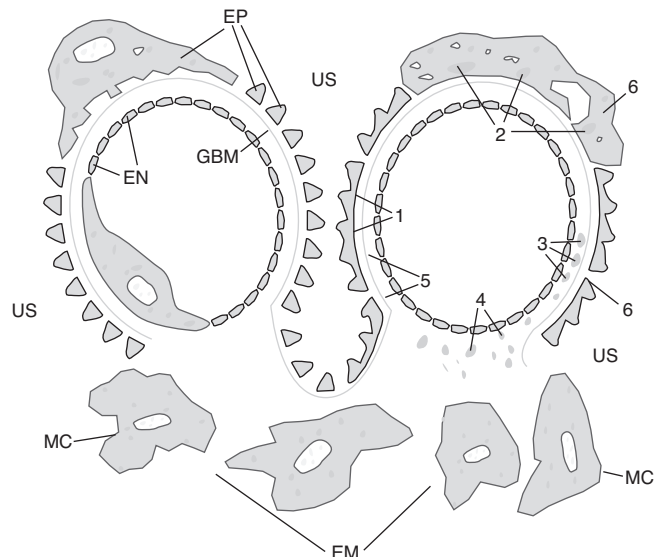
More severe disease in HIV patients.

Associated with multiple myeloma, chronic conditions, TB, rheumatic arthritis.

(LM = light microscopy; EM = electron microscopy; IF = immunofluorescence)

EP = epithelium with foot processes  
US = urinary space  
GBM = glomerular basement membrane  
EN = fenestrated endothelium  
MC = mesangial cells  
EM = extracellular matrix

- 1 = subepithelial deposits (membranous nephropathy)
- 2 = large irregular subepithelial deposits or “humps” (acute glomerulonephritis)
- 3 = subendothelial deposits in lupus glomerulonephritis
- 4 = mesangial deposits (IgA nephropathy)
- 5 = antibody binding to GBM—smooth linear pattern on immunofluorescence (Goodpasture’s)
- 6 = effacement of epithelial foot processes (common in all forms of glomerular injury with proteinuria)



<b>Kidney stones</b>	Can lead to severe complications, such as hydronephrosis and pyelonephritis. 4 major types:	
Calcium	Most common kidney stones (75–85%). Calcium oxalate (see Color Image 97), calcium phosphate, or both. Conditions that cause hypercalcemia (cancer, ↑ PTH, ↑ vitamin D, milk-alkali syndrome) can lead to hypercalciuria and stones. Tend to recur.	Radiopaque.
Ammonium magnesium phosphate (struvite)	2nd most common kidney stone. Caused by infection with urease-positive bugs ( <i>Proteus vulgaris</i> , <i>Staphylococcus</i> , <i>Klebsiella</i> ). Can form <b>staghorn calculi</b> that can be a nidus for UTIs.	Radiopaque. Worsened by alkaluria.
Uric acid	Strong association with hyperuricemia (e.g., gout). Often seen as a result of diseases with ↑ cell turnover, such as leukemia and myeloproliferative disorders.	Radiolucent. Worsened by aciduria.
Cystine	Most often 2° to cystinuria.	Faintly radiopaque.
<hr/>		
<b>Renal cell carcinoma</b>	Most common renal malignancy. Most common in men ages 50–70. ↑ incidence with smoking and obesity. Associated with von Hippel–Lindau and gene deletion in chromosome 3. Originates in renal tubule cells → polygonal clear cells. Manifests clinically with hematuria, palpable mass, 2° polycythemia, flank pain, fever, and weight loss. Invades IVC and spreads hematogenously. Associated with paraneoplastic syndromes (ectopic EPO, ACTH, PTHrP, and prolactin) (see Color Image 98).	
<hr/>		
<b>Wilms’ tumor</b>	Most common renal malignancy of early childhood (ages 2–4). Presents with huge, palpable flank mass, hemihypertrophy. Deletion of tumor suppression gene <i>WT1</i> on chromosome 11. Can be part of <b>WAGR</b> complex: <b>W</b> ilms’ tumor, <b>A</b> niridia, <b>G</b> enitourinary malformation, and <b>R</b> etardation.	
<hr/>		
<b>Transitional cell carcinoma</b>	Most common tumor of urinary tract system (can occur in renal calyces, renal pelvis, ureters, and bladder). Painless hematuria is suggestive of bladder cancer. Associated with problems in your <b>Pee SACS</b> : Phenacetin, Smoking, Aniline dyes, Cyclophosphamide, and Schistosomiasis (see Color Image 90).	
<hr/>		
<b>Pyelonephritis</b>		
Acute	Affects cortex with relative sparing of glomeruli/vessels. White cell casts in urine are pathognomonic (see Color Image 89A). Presents with fever, CVA tenderness.	
Chronic	Coarse, asymmetric corticomedullary scarring, blunted calyx. Tubules can contain eosinophilic casts (thyroidization of kidney) (see Color Image 89B).	
<hr/>		
<b>Diffuse cortical necrosis</b>	Acute generalized infarction of cortices of both kidneys. Likely due to a combination of vasospasm and DIC. Associated with obstetric catastrophes (e.g., abruptio placentae) and septic shock.	
<hr/>		
<b>Drug-induced interstitial nephritis</b>	Acute interstitial renal inflammation. Fever, rash, eosinophilia, hematuria 2 weeks after administration. Drugs (e.g., penicillin derivatives, NSAIDs, diuretics) act as haptens inducing hypersensitivity.	

**Acute tubular necrosis**

Most common cause of acute renal failure. Reversible, but fatal if left untreated.  
Associated with renal ischemia (e.g., shock), crush injury (myoglobinuria), toxins.  
Death most often occurs during initial oliguric phase. Recovery in 2–3 weeks.  
Loss of cell polarity, epithelial cell detachment, necrosis, granular casts. Three stages:  
inciting event → maintenance (low urine) → recovery.

**Renal papillary necrosis**

Associated with:

1. Diabetes mellitus
2. Acute pyelonephritis
3. Chronic phenacetin use (acetaminophen is phenacetin derivative)
4. Sickle cell anemia

**Acute renal failure**

Abrupt decline in renal function with ↑ creatinine and ↑ BUN over a period of several days.

1. Prerenal azotemia—decreased RBF (e.g., hypotension) → ↓ GFR.  $\text{Na}^+/\text{H}_2\text{O}$  retained by kidney.
2. Intrinsic renal—generally due to acute tubular necrosis or ischemia/toxins. Patchy necrosis leads to debris obstructing tubule and fluid backflow across necrotic tubule → ↓ GFR. Urine has epithelial/granular casts.
3. Postrenal—outflow obstruction (stones, BPH, neoplasia). Develops only with bilateral obstruction.

Variable	Prerenal	Renal	Postrenal
Urine osmolality	> 500	< 350	< 350
Urine Na	< 10	> 20	> 40
$\text{Fe}_{\text{Na}}$	< 1%	> 2%	> 4%
BUN/Cr ratio	> 20	< 15	> 15

**Consequences of renal failure**

Failure to make urine and excrete nitrogenous wastes.

Uremia—clinical syndrome marked by ↑ BUN and ↑ creatinine and associated symptoms.

Consequences:

1. Anemia (failure of erythropoietin production)
2. Renal osteodystrophy (failure of active vitamin D production)
3. Hyperkalemia, which can lead to cardiac arrhythmias
4. Metabolic acidosis due to ↓ acid secretion and ↓ generation of  $\text{HCO}_3^-$
5. Uremic encephalopathy
6. Sodium and  $\text{H}_2\text{O}$  excess → CHF and pulmonary edema
7. Chronic pyelonephritis
8. Hypertension

2 forms of renal failure—acute renal failure (often due to hypoxia) and chronic renal failure (e.g., due to hypertension and diabetes).

<b>Fanconi's syndrome</b>	Defect in proximal tubule transport of amino acids, glucose, phosphate, uric acid, protein, and electrolytes. Associated with rickets, osteomalacia, hypokalemia, metabolic acidosis.
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### Cysts

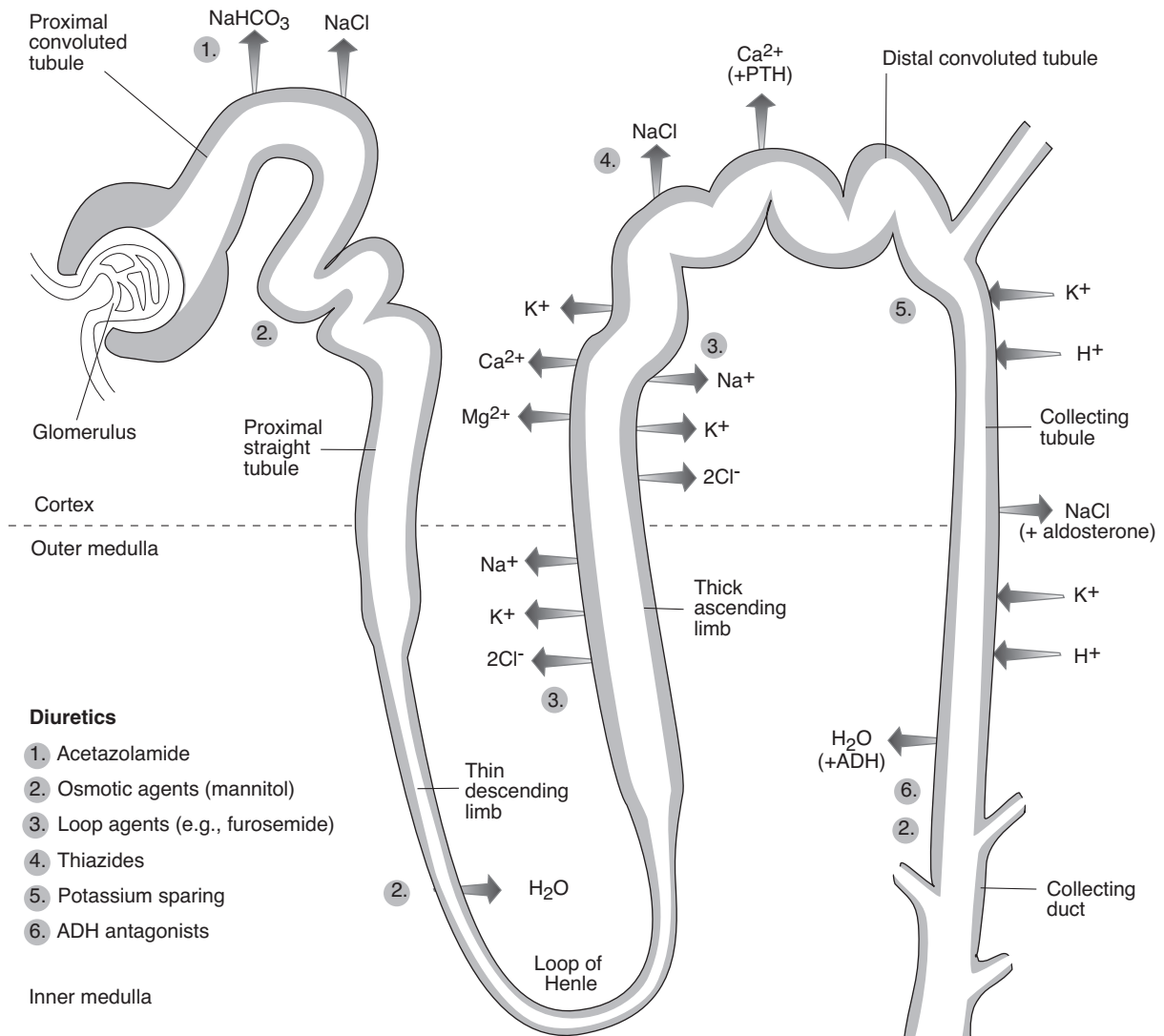
Adult polycystic kidney disease	Multiple, large, bilateral cysts that ultimately destroy the parenchyma. Presents with flank pain, hematuria, hypertension, urinary infection, progressive renal failure. Autosomal dominant mutation in APKD1. Death from uremia or hypertension. Associated with polycystic liver disease, berry aneurysms, mitral valve prolapse.
Infantile polycystic kidney disease	Infantile presentation in parenchyma. Autosomal recessive. Associated with hepatic cysts and fibrosis.
Dialysis cysts	Cortical and medullary cysts resulting from long-standing dialysis.
Simple cysts	Benign, incidental finding. Cortex only.
Medullary cystic disease	Medullary cysts. Ultrasound shows small kidney. Poor prognosis.
Medullary sponge disease	Collecting duct cysts. Good prognosis.

### Electrolyte disturbances

Electrolyte	Low serum concentration	High serum concentration
Na <sup>+</sup>	Disorientation, stupor, coma	Neurologic: irritability, delirium, coma
Cl <sup>-</sup>	2° to metabolic alkalosis	2° to non-anion gap acidosis
K <sup>+</sup>	U waves on ECG, flattened T waves, arrhythmias, paralysis	Peaked T waves, arrhythmias
Ca <sup>2+</sup>	Tetany, neuromuscular irritability	Delirium, renal stones, abdominal pain
Mg <sup>2+</sup>	Neuromuscular irritability, arrhythmias	Delirium, ↓ DTRs, cardiopulmonary arrest
PO <sub>4</sub> <sup>2-</sup>	Low-mineral ion product causes bone loss	High-mineral ion product causes metastatic calcification, renal stones



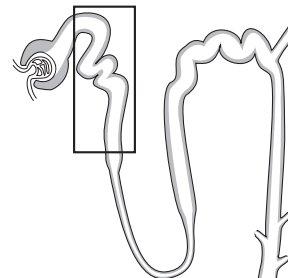
## Diuretics: site of action



(Adapted, with permission, from Katzung BG. *Basic and Clinical Pharmacology*, 7th ed. Stamford, CT: Appleton & Lange, 1997:243.)

**Mannitol**

Mechanism	Osmotic diuretic, $\uparrow$ tubular fluid osmolarity, producing $\uparrow$ urine flow.
Clinical use	Shock, drug overdose, $\downarrow$ intracranial/intraocular pressure.
Toxicity	Pulmonary edema, dehydration. Contraindicated in anuria, CHF.

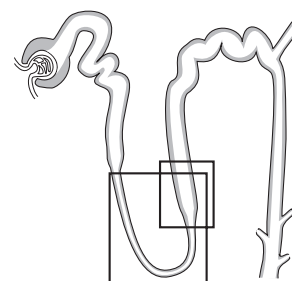
**Acetazolamide**

Mechanism	Carbonic anhydrase inhibitor. Causes self-limited $\text{NaHCO}_3$ diuresis and reduction in total-body $\text{HCO}_3^-$ stores.
Clinical use	Glaucoma, urinary alkalization, metabolic alkalosis, altitude sickness.
Toxicity	Hyperchloremic metabolic acidosis, neuropathy, $\text{NH}_3$ toxicity, sulfa allergy.

**ACID**azolamide causes  
**ACID**osis.

**Furosemide**

Mechanism	Sulfonamide loop diuretic. Inhibits cotransport system ( $\text{Na}^+$ , $\text{K}^+$ , $2\text{Cl}^-$ ) of thick ascending limb of loop of Henle. Abolishes hypertonicity of medulla, preventing concentration of urine. $\uparrow \text{Ca}^{2+}$ excretion. <b>Loops Lose</b> calcium.
Clinical use	Edematous states (CHF, cirrhosis, nephrotic syndrome, pulmonary edema), hypertension, hypercalcemia.
Toxicity	Ototoxicity, Hypokalemia, Dehydration, Allergy (sulfa), Nephritis (interstitial), Gout.



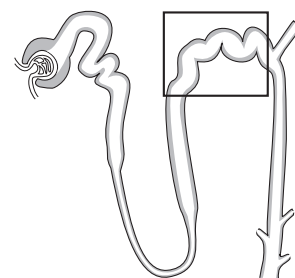
**OH DANG!**

**Ethacrynic acid**

Mechanism	Phenoxyacetic acid derivative (NOT a sulfonamide). Essentially same action as furosemide.
Clinical use	Diuresis in patients allergic to sulfa drugs.
Toxicity	Similar to furosemide; can be used in hyperuricemia, acute gout (never used to treat gout).

**Hydrochlorothiazide**

Mechanism	Thiazide diuretic. Inhibits $\text{NaCl}$ reabsorption in early distal tubule, reducing diluting capacity of the nephron. $\downarrow \text{Ca}^{2+}$ excretion.
Clinical use	Hypertension, CHF, idiopathic hypercalciuria, nephrogenic diabetes insipidus.
Toxicity	Hypokalemic metabolic alkalosis, hyponatremia, hyperGlycemia, hyperLipidemia, hyperUricemia, and hyperCalcemia. Sulfa allergy.



**HyperGLUC.**

**K<sup>+</sup>-sparing diuretics**

Mechanism

Spironolactone, Triamterene, Amiloride, eplerenone.  
Spironolactone is a competitive aldosterone receptor antagonist in the cortical collecting tubule.

Triamterene and amiloride act at the same part of the tubule by blocking Na<sup>+</sup> channels in the CCT.

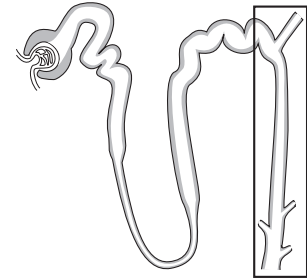
Clinical use

Hyperaldosteronism, K<sup>+</sup> depletion, CHF.

Toxicity

Hyperkalemia, endocrine effects (e.g., spironolactone causes gynecomastia, antiandrogen effects).

The K<sup>+</sup> STays.



**Diuretics: electrolyte changes**

Urine NaCl

↑ (all diuretics—carbonic anhydrase inhibitors, loop diuretics, thiazides, K<sup>+</sup>-sparing diuretics).

Urine K<sup>+</sup>

↑ (all except K<sup>+</sup>-sparing diuretics).

Blood pH

↓ (acidosis)—carbonic anhydrase inhibitors, K<sup>+</sup>-sparing diuretics; ↑ (alkalosis)—loop diuretics, thiazides.

Urine Ca<sup>+</sup>

↑ loop diuretics, ↓ thiazides.

**ACE inhibitors**

Mechanism

Captopril, enalapril, lisinopril.

Inhibit angiotensin-converting enzyme, reducing levels of angiotensin II and preventing inactivation of bradykinin, a potent vasodilator.

Renin release is ↑ due to loss of feedback inhibition.

**Losartan** is an angiotensin II receptor antagonist. It is **not** an ACE inhibitor and does not cause cough.

Clinical use

Hypertension, CHF, diabetic renal disease.

Toxicity

Cough, Angioedema, Proteinuria, Taste changes, hypOtension, Pregnancy problems (fetal renal damage), Rash, Increased renin, Lower angiotensin II. Also hyperkalemia. Avoid with bilateral renal artery stenosis.

**CAPTOPRIL.**

## ► REPRODUCTIVE—HIGH-YIELD CLINICAL VIGNETTES

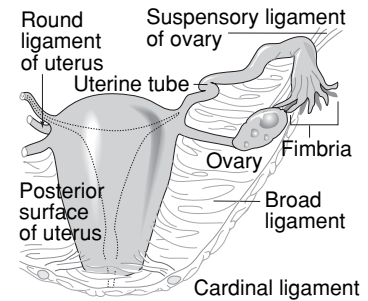
- |                                                                                                       |                                         |                                                                        |
|-------------------------------------------------------------------------------------------------------|-----------------------------------------|------------------------------------------------------------------------|
| ■ 24-year-old male develops testicular cancer.                                                        | Metastatic spread occurs by what route? | Para-aortic lymph nodes (recall descent of testes during development). |
| ■ Woman with previous cesarean section has a scar in her lower uterus close to the opening of the os. | What is she at ↑ risk for?              | Placenta previa.                                                       |
| ■ Obese woman presents with hirsutism and ↑ levels of serum testosterone.                             | What is the diagnosis?                  | Polycystic ovarian syndrome.                                           |
| ■ Pregnant woman at 16 weeks of gestation presents with an atypically large abdomen.                  | What is the diagnosis?                  | High hCG; hydatidiform mole.                                           |
| ■ 55-year-old postmenopausal woman is on tamoxifen therapy.                                           | What is she at ↑ risk of acquiring?     | Endometrial carcinoma.                                                 |

### Gonadal drainage

Venous drainage	Left ovary/testis → left gonadal vein → left renal vein → IVC Right ovary/testis → right gonadal vein → IVC
Lymphatic drainage	Ovaries/testes → para-aortic lymph nodes

### Ligaments of the uterus

Suspensory ligament of ovaries	Contains the ovarian vessels.
Transverse cervical (cardinal) ligament	Contains the uterine vessels.
Round ligament of uterus	Contains no important structures.
Broad ligament	Contains the round ligaments of the uterus and ovaries and the uterine tubules and vessels.



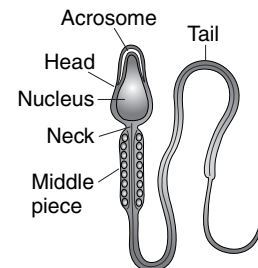
### Autonomic innervation of the male sexual response

Erection is mediated by the Parasympathetic nervous system.  
Emission is mediated by the Sympathetic nervous system.  
Ejaculation is mediated by visceral and somatic nerves.

Point and Shoot.

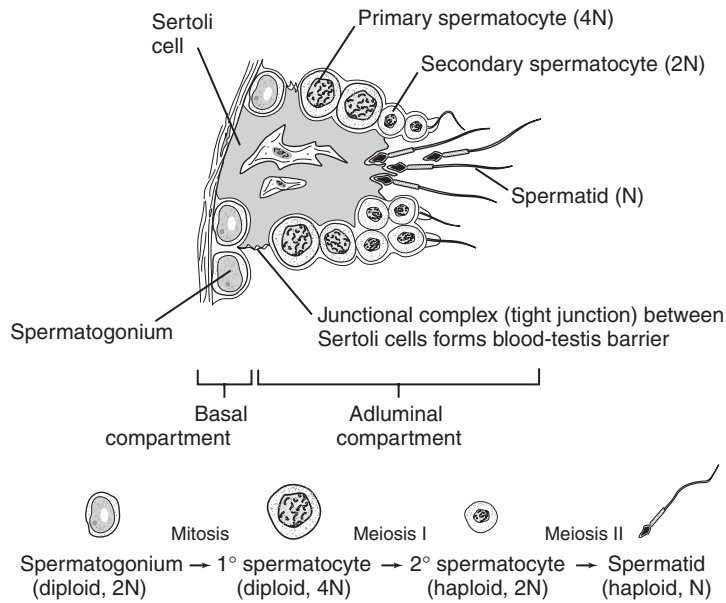
### Derivation of sperm parts

Acrosome is derived from the Golgi apparatus and flagellum (tail) from one of the centrioles. Middle piece (neck) has Mitochondria. Sperm food supply is fructose.



## Sperm development

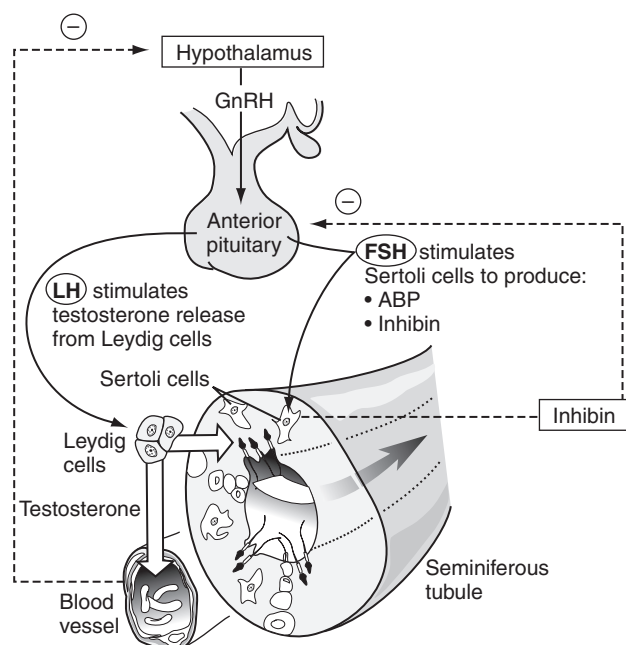
Spermatogenesis begins at puberty with spermatogonia (type A and type B). Full development takes 2 months. Spermatogenesis occurs in Seminiferous tubules. Blood-testis barrier is a physical barrier in the testis between the tissues responsible for spermatogenesis and the bloodstream (to avoid autoimmune response).



## SEVEN UP

Seminiferous tubules  
Epididymis  
Vas deferens  
Ejaculatory ducts  
(Nothing)  
Urethra  
Penis

## Male spermatogenesis



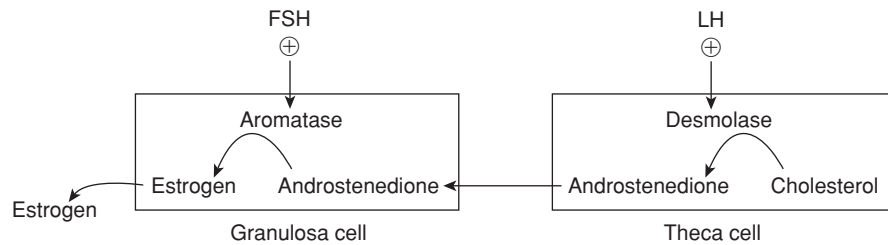
PRODUCTS	FUNCTIONS OF PRODUCTS
Androgen-binding protein (ABP)	Ensures that testosterone in seminiferous tubule is high
Inhibin	Inhibits FSH
Testosterone	Differentiates male genitalia, has anabolic effects on protein metabolism, maintains gametogenesis, maintains libido, inhibits GnRH, and fuses epiphyseal plates in bone.

FSH → Sertoli cells → Sperm production  
 LH → Leydig cell

<b>Androgens</b>	Testosterone, dihydrotestosterone (DHT), androstenedione.	
Source	DHT and testosterone (testis), androstenedione (adrenal).	Potency—DHT > testosterone > androstenedione.
Targets	Skin, prostate, seminal vesicles, epididymis, liver, muscle, brain.	Testosterone is converted to DHT by the enzyme 5 $\alpha$ -reductase, which is inhibited by finasteride.
Function	<ol style="list-style-type: none"> <li>1. Differentiation of wolffian duct system into internal gonadal structures</li> <li>2. 2° sexual characteristics and growth spurt during puberty</li> <li>3. Required for normal spermatogenesis</li> <li>4. Anabolic effects—↑ muscle size, ↑ RBC production</li> <li>5. ↑ libido</li> </ol>	Testosterone and androstenedione are converted to estrogen in adipose tissue by enzyme aromatase.

## Estrogen

Source	Ovary (estradiol), placenta (estriol), blood (aromatization).	Potency—estradiol > estrone > estriol.
Function	<ol style="list-style-type: none"> <li>1. Growth of follicle</li> <li>2. Endometrial proliferation, myometrial excitability</li> <li>3. Development of genitalia</li> <li>4. Stromal development of breast</li> <li>5. Female fat distribution</li> <li>6. Hepatic synthesis of transport proteins</li> <li>7. Feedback inhibition of FSH</li> <li>8. LH surge (estrogen feedback on LH secretion switches to positive from negative just before LH surge)</li> <li>9. ↑ myometrial excitability</li> <li>10. ↑ HDL, ↓ LDL</li> </ol>	Pregnancy: 50-fold ↑ in estradiol and estrone 1000-fold ↑ in estriol (indicator of fetal well being)

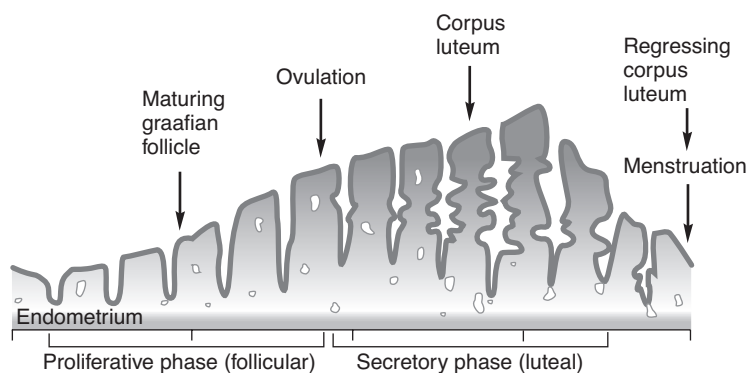


## Progesterone

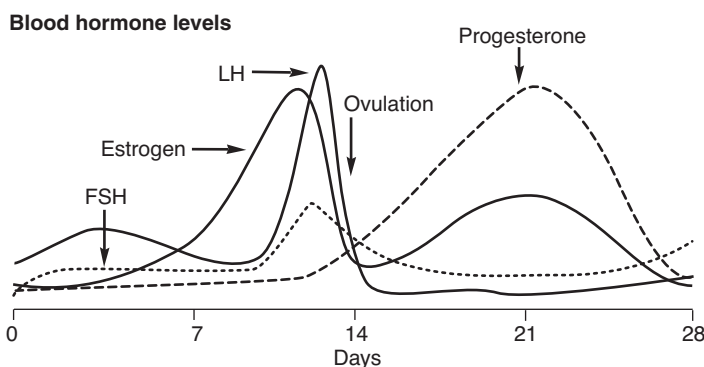
Source	Corpus luteum, placenta, adrenal cortex, testes.	Elevation of progesterone is indicative of ovulation.
Function	<ol style="list-style-type: none"> <li>1. Stimulation of endometrial glandular secretions and spiral artery development</li> <li>2. Maintenance of pregnancy</li> <li>3. ↓ myometrial excitability</li> <li>4. Production of thick cervical mucus, which inhibits sperm entry into the uterus</li> <li>5. ↑ body temperature</li> <li>6. Inhibition of gonadotropins (LH, FSH)</li> <li>7. Uterine smooth muscle relaxation</li> </ol>	Progesterone Prepares for Pregnancy.



## Menstrual cycle



Follicular growth is fastest during 2nd week of proliferative phase.  
 Estrogen stimulates endometrial proliferation.  
 Progesterone maintains endometrium to support implantation.  
 $\downarrow$  progesterone leads to  $\downarrow$  fertility.



## Ovulation

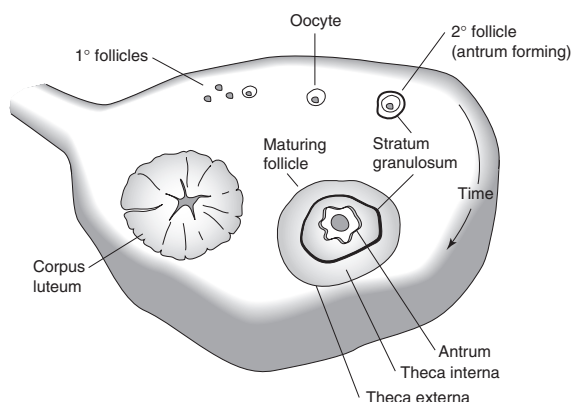
Estrogen surge day before ovulation.  
 Stimulates LH, inhibits FSH.  
 LH surge causes ovulation (rupture of follicle).  
 $\uparrow$  temperature (progesterone induced).  
 Ferning of cervical mucosa.  
 Oral contraceptives prevent estrogen surge, LH surge  $\rightarrow$  ovulation does not occur.

Mittelschmerz—blood from ruptured follicle causes peritoneal irritation that can mimic appendicitis.

## Meiosis and ovulation

1° oocytes begin meiosis I during fetal life and complete meiosis I just prior to ovulation.  
 Meiosis I is arrested in proPhase for years until Ovulation.  
 Meiosis II is arrested in METaphase until fertilization.

An egg MET a sperm.



► REPRODUCTIVE—PHYSIOLOGY (*continued*)**hCG**

Source	Syncytiotrophoblast of placenta.
Function	<ol style="list-style-type: none"> <li>1. Maintains the corpus luteum for the 1st trimester by acting like LH. In the 2nd and 3rd trimester, the placenta synthesizes its own estrogen and progesterone and the corpus luteum degenerates.</li> <li>2. Used to detect pregnancy because it appears in the urine 8 days after successful fertilization (blood and urine tests available).</li> <li>3. Elevated hCG in women with hydatidiform moles or choriocarcinoma.</li> </ol>

**Menopause**

Cessation of estrogen production with age-linked decline in number of ovarian follicles. Average age of onset is 51 years (earlier in smokers).

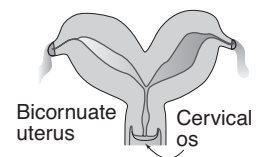
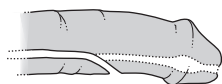
Hormonal changes:  
 ↓ estrogen, ↑↑ FSH, ↑ LH (no surge), ↑ GnRH.

Menopause causes **HAVOC**:  
**H**ot flashes, **A**trophy of the Vagina, **O**steoporosis, **C**oronary artery disease.

## ► REPRODUCTIVE—PATHOLOGY

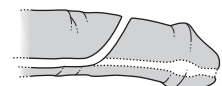
**Bicornuate uterus**

Results from incomplete fusion of the paramesonephric ducts. Associated with urinary tract abnormalities and infertility.

**Congenital penile abnormalities****Hypospadias**

Abnormal opening of penile urethra on inferior (ventral) side of penis due to failure of urethral folds to close.

Hypospadias is more common than epispadias. Fix hypospadias to prevent UTIs.

**Epispadias**

Abnormal opening of penile urethra on superior (dorsal) side of penis due to faulty positioning of genital tubercle.

Exstrophy of the bladder is associated with epispadias.

**Sex chromosome disorders**

Klinefelter's syndrome  
 [male] (XYY),  
 1:850

Testicular atrophy, eunuchoid body shape, tall, long extremities, gynecomastia, female hair distribution. Presence of inactivated X chromosome (Barr body). (see Image 107). Common cause of hypogonadism seen in infertility workup.

Dysgenesis of seminiferous tubules → ↓ inhibin → ↑ FSH  
 Abnormal Leydig cell function  
 → ↓ testosterone → ↑ LH  
 → ↑ estrogen

Turner's syndrome  
 [female] (XO),  
 1:3000

Short stature, ovarian dysgenesis (streak ovary), webbing of neck, coarctation of the aorta, most common cause of 1° amenorrhea. No Barr body. (see Image 108).

“Hugs and kisses” (XO) from Tina **Turner** (female).

Double Y males  
 [male] (XYY),  
 1:1000

Phenotypically normal, very tall, severe acne, antisocial behavior (seen in 1–2% of XYY males). Normal fertility.

Observed with ↑ frequency among inmates of penal institutions.

<b>Pseudohermaphroditism</b>	
	Disagreement between the phenotypic (external genitalia) and gonadal (testes vs. ovaries) sex.
Female pseudo-hermaphrodite (XX)	Ovaries present, but external genitalia are virilized or ambiguous. Due to excessive and inappropriate exposure to androgenic steroids during early gestation (i.e., congenital adrenal hyperplasia or exogenous administration of androgens during pregnancy).
Male pseudo-hermaphrodite (XY)	Testes present, but external genitalia are female or ambiguous. Most common form is androgen insensitivity syndrome (testicular feminization).
<hr/>	
<b>True hermaphrodite (46,XX or 47,XXY)</b>	Both ovary and testicular tissue present; ambiguous genitalia. Very rare.
<hr/>	
<b>Androgen insensitivity syndrome (46,XY)</b>	Defect in androgen receptor resulting in normal-appearing female; female external genitalia with rudimentary vagina; uterus and uterine tubes generally absent; develops testes (often found in labia majora; surgically removed to prevent malignancy). Levels of testosterone, estrogen, and LH are all high.
<hr/>	
<b>5<math>\alpha</math>-reductase deficiency</b>	Unable to convert testosterone to DHT. Ambiguous genitalia until puberty, when $\uparrow$ testosterone causes masculinization of genitalia. Testosterone/estrogen levels are normal; LH is normal or $\uparrow$ .
<hr/>	
<b>Hydatidiform mole</b>	A pathologic ovum (“empty egg”—ovum with no DNA) resulting in cystic swelling of chorionic villi and proliferation of chorionic epithelium (trophoblast). Most common precursor of choriocarcinoma. High $\beta$ -hCG. “Honeycombed uterus,” “cluster of grapes” appearance. Enlarged uterus. Genotype of a <b>complete</b> mole is 46,XX and is <b>completely</b> paternal in origin (no maternal chromosomes); no associated fetus. <b>PART</b> ial mole is made up of 3 or more <b>PARTS</b> (triploid or tetraploid); may contain fetal <b>PARTS</b> (see Color Image 74).
<hr/>	
<b>Pregnancy-induced hypertension (preeclampsia-eclampsia)</b>	Preeclampsia is the triad of hypertension, proteinuria, and edema; eclampsia is the addition of seizures to the triad. Affects 7% of pregnant women from 20 weeks’ gestation to 6 weeks postpartum. $\uparrow$ incidence in patients with preexisting hypertension, diabetes, chronic renal disease, and autoimmune disorders. Etiology involves placental ischemia. Can be associated with HELLP syndrome ( <b>H</b> emolysis, <b>E</b> levated <b>LFTs</b> , <b>L</b> ow <b>P</b> latelets).
Clinical features	Headache, blurred vision, abdominal pain, edema of face and extremities, altered mentation, hyperreflexia; lab findings may include thrombocytopenia, hyperuricemia.
Treatment	Delivery of fetus as soon as viable. Otherwise bed rest, salt restriction, and monitoring and treatment of hypertension. For eclampsia, a medical emergency, IV magnesium sulfate and diazepam.
<hr/>	

**Pregnancy complications**

1. Abruptio placentae—premature detachment of placenta from implantation site. **Painful** uterine bleeding (usually during 3rd trimester). Fetal death. May be associated with DIC. ↑ risk with smoking, hypertension, cocaine use.
2. Placenta accreta—defective decidual layer allows placenta to attach directly to myometrium. Predisposed by prior C-section or inflammation. May have massive hemorrhage after delivery.
3. Placenta previa—attachment of placenta to lower uterine segment. May occlude cervical os. **Painless** bleeding in any trimester.
4. Ectopic pregnancy—most often in fallopian tubes, predisposed by salpingitis (PID). Suspect with ↑ hCG and sudden lower abdominal pain; confirm with ultrasound. Often clinically mistaken for appendicitis.

**Amniotic fluid abnormalities**

- |                 |                                                                                                                                                       |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------|
| Polyhydramnios  | > 1.5–2 L of amniotic fluid; associated with esophageal/duodenal atresia, causing inability to swallow amniotic fluid, and with anencephaly.          |
| Oligohydramnios | < 0.5 L of amniotic fluid; associated with bilateral renal agenesis or posterior urethral valves (in males) and resultant inability to excrete urine. |

**Cervical pathology**

- |                                 |                                                                                                                                                                                                                                             |
|---------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Dysplasia and carcinoma in situ | Disordered epithelial growth; begins at basal layer and extends outward. Classified as CIN 1, CIN 2, or CIN 3 (carcinoma in situ), depending on extent of dysplasia. Associated with HPV 16, 18. May progress slowly to invasive carcinoma. |
| Invasive carcinoma              | Often squamous cell carcinoma. Pap smear can catch cervical dysplasia (koilocytes) before it progresses to invasive carcinoma. Lateral invasion can block ureters, causing renal failure.                                                   |

**Uterine pathology**

- |                         |                                                                                                                                                                                                                                                                                                                                                        |
|-------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Endometriosis           | Non-neoplastic endometrial glands/stroma in abnormal locations outside the uterus. Characterized by cyclic bleeding (menstrual type) from ectopic endometrial tissue resulting in blood-filled “chocolate cysts.” In ovary or on peritoneum. Manifests clinically as severe menstrual-related pain. Often results in infertility (see Color Image 77). |
| Adenomyosis             | Endometriosis within the myometrium.                                                                                                                                                                                                                                                                                                                   |
| Endometrial hyperplasia | Abnormal endometrial gland proliferation usually caused by excess estrogen stimulation. ↑ risk for endometrial carcinoma. Most commonly manifests clinically as vaginal bleeding.                                                                                                                                                                      |
| Endometrial carcinoma   | Most common gynecologic malignancy. Peak age 55–65 years old. Clinically presents with vaginal bleeding. Typically preceded by endometrial hyperplasia. Risk factors include prolonged use of estrogen without progestins, obesity, diabetes, hypertension, nulliparity, and late menopause.                                                           |
| Leiomyoma               | Most common of all tumors in females. Often presents with multiple tumors with well demarcated borders. ↑ incidence in blacks. Benign smooth muscle tumor; malignant transformation is rare. Estrogen sensitive—tumor size ↑ with pregnancy and ↓ with menopause. Does not progress to leiomyosarcoma (see Image 122).                                 |
| Leiomyosarcoma          | Bulky irregularly shaped tumor with areas of necrosis and hemorrhage, typically arising de novo (not from leiomyoma). ↑ incidence in blacks. Highly aggressive tumor with tendency to recur. May protrude from cervix and bleed.                                                                                                                       |

<b>Polycystic ovarian syndrome</b>	<p>↑ LH, ↓ FSH, ↑ testosterone. ↑ LH production leads to anovulation, hyperandrogenism due to deranged steroid synthesis. Manifest clinically by amenorrhea, infertility, obesity, and hirsutism. Treat with weight loss, OCPs, gonadotropin analogs, or surgery.</p>
<b>Ovarian cysts</b>	<ol style="list-style-type: none"> <li>1. Follicular cyst—distention of unruptured graafian follicle. May be associated with hyperestrinism and endometrial hyperplasia.</li> <li>2. Corpus luteum cyst—hemorrhage into persistent corpus luteum. Menstrual irregularity.</li> <li>3. Theca-lutein cyst—often bilateral/multiple. Due to gonadotropin stimulation. Associated with choriocarcinoma and moles.</li> <li>4. “Chocolate cyst”—blood-containing cyst from ovarian endometriosis. Varies with menstrual cycle.</li> </ol>
<b>Ovarian germ cell tumors</b>	
Dysgerminoma	Malignant, equivalent to male seminoma. Sheets of uniform cells. ↑ hCG.
Yolk sac (endodermal sinus tumor)	Aggressive malignancy in ovaries (testes in boys) and sacrococcygeal area of young children. ↑ AFP.
Choriocarcinoma	Rare but malignant; can develop during pregnancy in mother or baby. Large, hyperchromatic syncytiotrophoblastic cells. ↑ hCG.
Teratoma	<p>90% of ovarian germ cell tumors. Contain cells from 2 or 3 germ layers.</p> <p>Mature teratoma (“dermoid cyst”)—most frequent benign ovarian tumor.</p> <p>Immature teratoma—aggressively malignant.</p> <p>Struma ovarii—contains functional thyroid tissue (see Images 123, 124).</p>
<b>Ovarian non-germ cell tumors</b>	<ol style="list-style-type: none"> <li>1. Serous cystadenoma—20% of ovarian tumors. Frequently bilateral, lined with fallopian tube-like epithelium. Benign.</li> <li>2. Serous cystadenocarcinoma—50% ovarian tumors, malignant and frequently bilateral.</li> <li>3. Mucinous cystadenoma—multilocular cyst lined by mucus-secreting epithelium. Benign.</li> <li>4. Mucinous cystadenocarcinoma—malignant. Pseudomyxoma peritonei—intraperitoneal accumulation of mucinous material from ovarian or appendiceal tumor.</li> <li>5. Brenner tumor—benign tumor that resembles Bladder epithelium.</li> <li>6. Ovarian fibroma—bundles of spindle-shaped fibroblasts. Meigs’ syndrome—triad of ovarian fibroma, ascites, and hydrothorax.</li> <li>7. Granulosa cell tumor—secretes estrogen → precocious puberty (kids). Can cause endometrial hyperplasia or carcinoma in adults. Call-Exner bodies—small follicles filled with eosinophilic secretions.</li> </ol>

## Breast tumors

### Type

Benign tumors

### Characteristics

1. Fibroadenoma—most common tumor < 25 years. Small, mobile, firm mass with sharp edges. ↑ size and tenderness with pregnancy. Not a precursor to breast cancer.
2. Intraductal papilloma—tumor of lactiferous ducts; presents with serous or bloody nipple discharge.
3. Cystosarcoma phyllodes—large, bulky mass of connective tissue and cysts. Tumor may have “leaflike” projections. Some may be malignant.

Malignant tumors  
(carcinoma)

Common postmenopause. Arise from mammary duct epithelium or lobular glands. Overexpression of estrogen/progesterone receptors or *erb-B2* (HER-2, an EGF receptor) is common; affects therapy and prognosis. Lymph node involvement is the single most important prognostic factor.

Histologic types:

1. Ductal carcinoma in situ (DCIS)—early malignancy without basement membrane penetration.
2. Invasive ductal, no specific type—firm, fibrous mass. The worst and most invasive. Common.
3. Comedocarcinoma—ductal, with cheesy consistency due to central necrosis.
4. Inflammatory—lymphatic involvement; poor prognosis.
5. Invasive lobular—often multiple, bilateral.
6. Medullary—fleshy, cellular, lymphocytic infiltrate. Good prognosis.
7. Paget’s disease of the breast—eczematous patches on nipple. Paget cells—large cells with clear halo; suggest underlying carcinoma. Also seen on vulva.

Risk factors: gender, age, early 1st menarche (< 12 years old), delayed 1st pregnancy (> 30 years old), late menopause (> 50 years old), family history of 1st-degree relative with breast cancer at a young age. Risk is NOT increased by fibroadenoma or nonhyperplastic cysts.

## Common breast conditions

Fibrocystic disease

Most common cause of “breast lumps” age 25–menopause. Presents with diffuse breast pain and multiple lesions, often bilateral. Usually does not indicate ↑ risk of carcinoma. Histologic types:

1. Fibrosis—hyperplasia of breast stroma.
2. Cystic—fluid filled.
3. Sclerosing—↑ acini and intralobular fibrosis.
4. Epithelial hyperplasia—↑ in number of epithelial cell layers in terminal duct lobule. ↑ risk of carcinoma with atypical cells. Occurs > 30 years.

Acute mastitis

Breast abscess; during breast-feeding ↑ risk of bacterial infection through cracks in the nipple; *Staphylococcus aureus* is the most common pathogen.

Fat necrosis

A benign painless lump; forms due to injury to breast tissue.

Gynecomastia

Results from hyperestrogenism (cirrhosis, testicular tumor, puberty, old age), Klinefelter’s syndrome, or drug induced (cimetidine, alcohol abuse, marijuana, heroin, psychoactive drugs, digitalis).

**Prostate pathology**

Prostatitis      Dysuria, frequency, urgency, low back pain. Acute: bacterial; chronic: bacterial or abacterial (most common).

**Benign prostatic hyperplasia**

Common in men > 50 years of age. May be due to an age-related increase in estradiol with possible sensitization of the prostate to the growth-promoting effects of DHT. Characterized by a nodular enlargement of the periurethral (lateral and middle) lobes of the prostate gland, compressing the urethra into a vertical slit. Often presents with ↑ frequency of urination, nocturia, difficulty starting and stopping the stream of urine, and dysuria. May lead to distention and hypertrophy of the bladder, hydronephrosis, and UTIs. Not considered a premalignant lesion. ↑ free prostate-specific antigen (PSA).

**Prostatic adenocarcinoma**

Common in men > 50 years of age. Arises most often from the posterior lobe (peripheral zone) of the prostate gland and is most frequently diagnosed by digital rectal examination (hard nodule) and prostate biopsy. Prostatic acid phosphatase and PSA are useful tumor markers (↑ total PSA, with ↓ fraction of free PSA). Osteoblastic metastases in bone may develop in late stages, as indicated by an ↑ in serum alkaline phosphatase and PSA.

**Cryptorchidism**

Undescended testis (one or both); lack of spermatogenesis due to ↑ body temperature; associated with ↑ risk of germ cell tumors.

**Testicular germ cell tumors**

~95% of all testicular tumors

Seminoma      Malignant; painless testicular enlargement; most common testicular tumor, mostly affecting males age 15–35.

Embryonal carcinoma      Malignant; painful; worse prognosis than seminoma.

Yolk sac (endodermal sinus) tumor      Analogous to ovarian yolk sac tumor (↑ AFP).

Choriocarcinoma      Malignant, ↑ hCG.

Teratoma      Unlike in females, mature teratoma in males is most often malignant.

**Testicular non-germ cell tumors**

Leydig cell      Benign, contains Reinke crystals; usually androgen producing, gynecomastia in men, precocious puberty in boys.

Sertoli cell      Benign, androblastoma from sex cord stroma.

Testicular lymphoma      Most common testicular cancer in older men.

► REPRODUCTIVE–PATHOLOGY (*continued*)**Penile pathology**

Carcinoma in situ:	
Bowen disease	Solitary crusty plaque, usually on the shaft of the penis or on the scrotum; peak incidence in fifth decade of life; becomes invasive SCC in <10% of cases.
Erythroplasia of Queyrat	Red velvety plaques, usually involving the glans; otherwise similar to Bowen disease
Bowenoid papulosis	Multiple papular lesions; affects younger age group than the other two; usually does not become invasive.
Squamous cell carcinoma (SCC)	Rare in circumcised men; uncommon in US and Europe, more common in Asia, Africa, and South America. Commonly associated with HPV.

## ► REPRODUCTIVE–PHARMACOLOGY

**Antiandrogens**

Finasteride	A 5 $\alpha$ -reductase inhibitor ( $\downarrow$ conversion of testosterone to dihydrotestosterone). Useful in BPH. Also promotes hair growth—used to treat male-pattern baldness.
Flutamide	A nonsteroidal competitive inhibitor of androgens at the testosterone receptor. Used in prostate carcinoma.
Ketoconazole, spironolactone	Inhibit steroid synthesis; used in the treatment of polycystic ovarian syndrome to prevent hirsutism.

**Leuprolide**

Mechanism	GnRH analog with agonist properties when used in pulsatile fashion; antagonist properties when used in continuous fashion.	When used in continuous fashion, it causes a transient initial burst of LH and FSH.
Clinical use	Infertility (pulsatile), prostate cancer (continuous—use with flutamide), uterine fibroids.	
Toxicity	Antiandrogen, nausea, vomiting.	

**Sildenafil, vardenafil**

Mechanism	Inhibit cGMP phosphodiesterase, causing $\uparrow$ cGMP, smooth muscle relaxation in the corpus cavernosum, $\uparrow$ blood flow, and penile erection.	Sildenafil and vardenafil fill the penis.
Clinical use	Treatment of erectile dysfunction.	
Toxicity	Headache, flushing, dyspepsia, blue-green color vision. Risk of life-threatening hypotension in patients taking nitrates.	

**Clomiphene**

Mechanism	A partial agonist at estrogen receptors in the pituitary gland. Prevents normal feedback inhibition and $\uparrow$ release of LH and FSH from the pituitary, which stimulates ovulation.
Clinical use	Treatment of infertility.
Toxicity	Hot flashes, ovarian enlargement, multiple simultaneous pregnancies, visual disturbances.



**Mifepristone (RU-486)**

Mechanism	Competitive inhibitor of progestins at progesterone receptors.
Clinical use	Postcoital abortifacient (prevents implantation).
Toxicity	Heavy bleeding, GI effects (nausea, vomiting, anorexia), abdominal pain.

**Oral contraception  
(synthetic  
progestins,  
estrogen)****Advantages**

Reliable (< 1% failure)  
 ↓ risk of endometrial and ovarian cancer  
 ↓ incidence of ectopic pregnancy  
 ↓ pelvic infections  
 Regulation of menses

**Disadvantages**

Taken daily  
 No protection against STDs  
 ↑ triglycerides  
 Depression, weight gain, nausea, hypertension  
 Hypercoagulable state

**Hormone replacement  
therapy (HRT)**

Used for relief or prevention of menopausal symptoms (hot flashes, vaginal atrophy, etc.) and osteoporosis (due to diminished estrogen levels).  
 Unopposed estrogen replacement therapy (ERT) increases the risk of endometrial cancer, so progesterone is added.

## ► RESPIRATORY—HIGH-YIELD CLINICAL VIGNETTES

- |                                                                                                                                                                          |                                     |                           |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------|---------------------------|
| ■ Patient exhibits an extended expiratory phase.                                                                                                                         | What is the disease process?        | Obstructive lung disease. |
| ■ Tall, thin male teenager has abrupt-onset dyspnea and left-sided chest pain. There is hyperresonant percussion on the affected side, and breath sounds are diminished. | What is the diagnosis?              | Spontaneous pneumothorax. |
| ■ Young man is concerned about his wife's inability to conceive and her recurrent URIs. She has dextrocardia.                                                            | Which of her proteins is defective? | Dynein (Kartagener's).    |

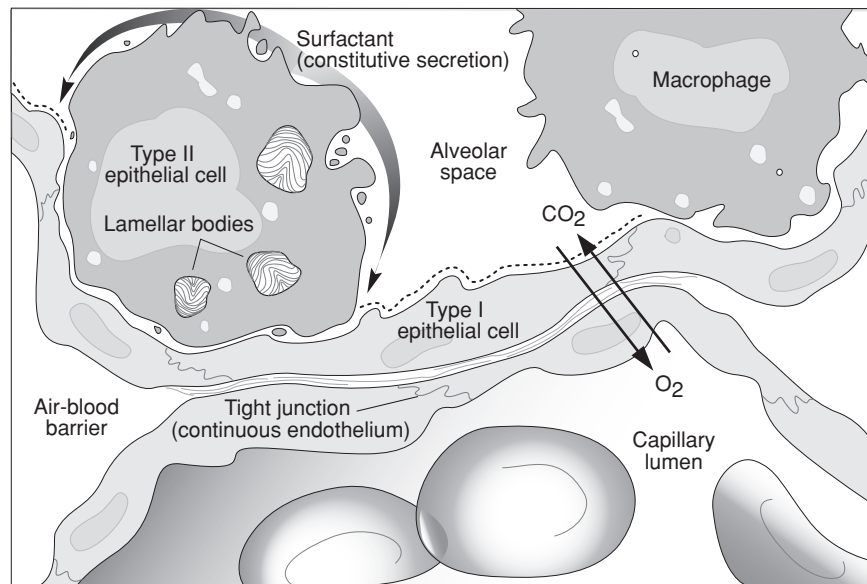
## Respiratory tree

Conducting zone	Consists of nose, pharynx, trachea, bronchi, bronchioles, and terminal bronchioles. Brings air in and out. Warms, humidifies, filters air. Anatomic dead space. Walls of conducting airways contain smooth muscle.
Respiratory zone	Consists of respiratory bronchioles, alveolar ducts, and alveoli. Participates in gas exchange.

## Pneumocytes

Pseudocolumnar ciliated cells extend to the respiratory bronchioles; goblet cells extend only to the terminal bronchioles.	Mucus secretions are swept out of the lungs toward the mouth by ciliated cells.
Type I cells (97% of alveolar surfaces) line the alveoli.	A lecithin-to-sphingomyelin ratio of > 2.0 in amniotic fluid is indicative of fetal lung maturity.
Type II cells (3%) secrete pulmonary surfactant (dipalmitoyl phosphatidylcholine), which ↓ the alveolar surface tension. Also serve as precursors to type I cells and other type II cells. Type II cells proliferate during lung damage.	

## Gas exchange barrier



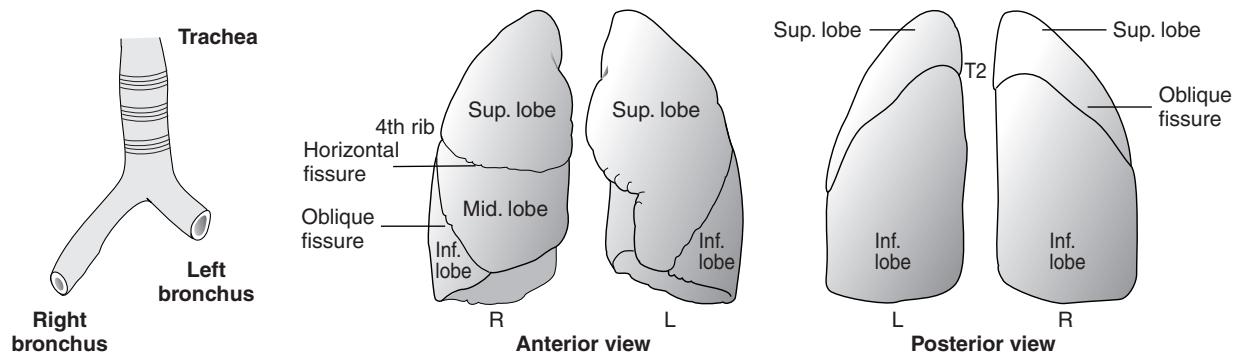
## Bronchopulmonary segments

Each bronchopulmonary segment has a 3° (segmental) bronchus and 2 arteries (bronchial and pulmonary) in the center; veins and lymphatics drain along the borders.	Arteries run with Airways.
-------------------------------------------------------------------------------------------------------------------------------------------------------------------	----------------------------

## Lung relations

Right lung has 3 lobes; Left has 2 lobes and Lingula (homologue of right middle lobe). Right lung is more common site for inhaled foreign body owing to less acute angle of right main stem bronchus.

Instead of a middle lobe, the left lung has a space occupied by the heart. The relation of the pulmonary artery to the bronchus at each lung hilus is described by **RALS**—**R**ight **A**nterior; **L**eft **S**uperior.



## Diaphragm structures

Structures perforating diaphragm:

At T8: IVC.

At T10: esophagus, vagus (2 trunks).

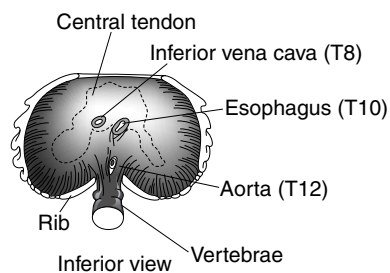
At T12: aorta (red), thoracic duct (white), azygous vein (blue).

Diaphragm is innervated by C3, 4, and 5 (phrenic nerve). Pain from the diaphragm can be referred to the shoulder.

I 8 10 EGGs AT 12:

I = IVC @ 8th vertebra; EG = Esophagus; G = vagus @ 10th vertebra; A = Aorta, Azygous; T = Thoracic duct @ 12th vertebra.

“C3, 4, 5 keeps the diaphragm alive.”



## Muscles of respiration

Quiet breathing:

Inspiration—diaphragm.

Expiration—passive.

Exercise:

Inspiration—external intercostals, scalene muscles, sternomastoids.

Expiration—rectus abdominis, internal and external obliques, transversus abdominis, internal intercostals.

### Important lung products

1. Surfactant—produced by type II pneumocytes, ↓ alveolar surface tension, ↑ compliance
2. Prostaglandins
3. Histamine ↑ bronchoconstriction
4. Angiotensin-converting enzyme (ACE)—angiotensin I → angiotensin II; inactivates bradykinin (ACE inhibitors ↑ bradykinin and cause cough, angioedema)
5. Kallikrein—activates bradykinin

**Surfactant**—dipalmitoyl phosphatidylcholine (lecithin) deficient in neonatal RDS.

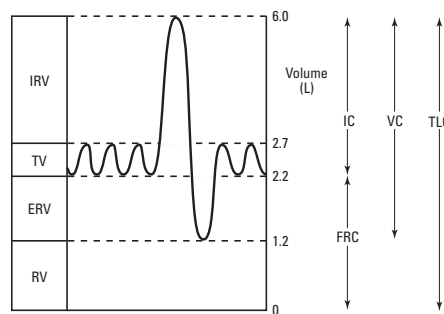
$$\text{Collapsing pressure} = \frac{2 (\text{tension})}{\text{radius}}$$

### Lung volumes

1. Residual volume (RV)—air in lung after maximal expiration
2. Expiratory reserve volume (ERV)—air that can still be breathed out after normal expiration
3. Tidal volume (TV)—air that moves into lung with each quiet inspiration, typically 500 mL
4. Inspiratory reserve volume (IRV)—air in excess of tidal volume that moves into lung on maximum inspiration
5. Vital capacity (VC)—TV + IRV + ERV
6. Functional reserve capacity (FRC)—RV + ERV (volume in lungs after normal expiration)
7. Inspiratory capacity (IC)—IRV + TV
8. Total lung capacity—TLC = IRV + TV + ERV + RV

Vital capacity is everything but the residual volume.

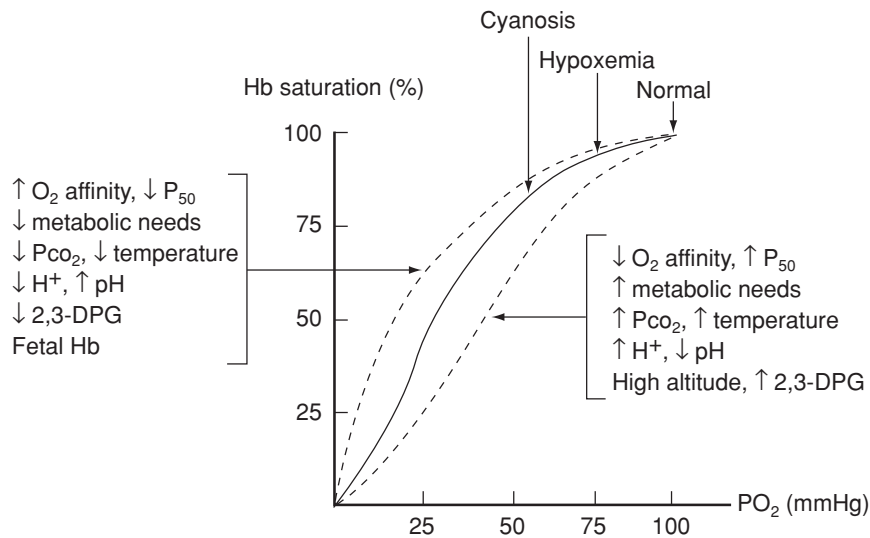
A capacity is a sum of ≥ 2 volumes.



### Determination of physiologic dead space

$$V_D = V_T \times \frac{(P_{aCO_2} - P_{eCO_2})}{P_{aCO_2}}$$

$P_{aCO_2}$  = arterial  $PCO_2$ ,  $P_{eCO_2}$  = expired air  $PCO_2$ .

**Oxygen-hemoglobin dissociation curve**

When curve shifts to the right,  
 ↓ affinity of hemoglobin  
 for O<sub>2</sub> (facilitates unloading  
 of O<sub>2</sub> to tissue).

An ↑ in all factors (except pH)  
 causes a shift of the curve  
 to the right.

A ↓ in all factors (except pH)  
 causes a shift of the curve to  
 the left.

**Right shift—CADET face right:**

CO<sub>2</sub>  
 Acid/Altitude  
 DPG (2,3-DPG)  
 Exercise  
 Temperature

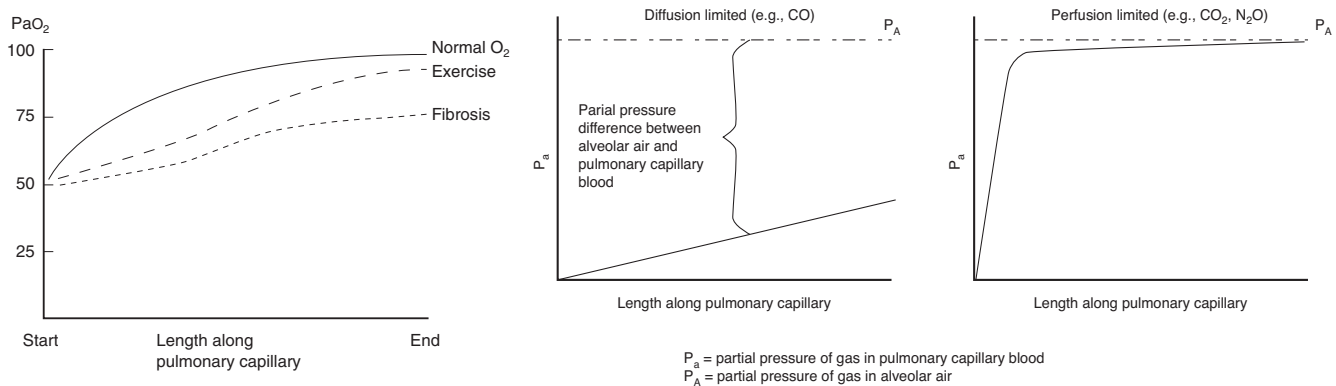
**Pulmonary circulation**

Normally a low-resistance, high-compliance system.

PO<sub>2</sub> and PCO<sub>2</sub> exert opposite effects on pulmonary and systemic circulation. A ↓ in PaO<sub>2</sub> causes a hypoxic vasoconstriction that shifts blood away from poorly ventilated regions of lung to well-ventilated regions of lung.

1. Perfusion limited—O<sub>2</sub> (normal health), CO<sub>2</sub>, N<sub>2</sub>O. Gas equilibrates early along the length of the capillary. Diffusion can be ↑ only if blood flow ↑.
2. Diffusion limited—O<sub>2</sub> (exercise, emphysema, fibrosis), CO. Gas does not equilibrate by the time blood reaches the end of the capillary.

A consequence of pulmonary hypertension is cor pulmonale and subsequent right ventricular failure (jugular venous distention, edema, hepatomegaly).



**Pulmonary hypertension**

Normal pulmonary artery pressure = 10–14 mm Hg; pulmonary HTN  $\geq 25$  mm Hg or  $>35$  mm Hg during exercise.

Primary—unknown etiology, poor prognosis.

Secondary—usually caused by COPD, also can be caused by L  $\rightarrow$  R shunt.

**Pulmonary vascular resistance (PVR)**

$$\text{PVR} = \frac{P_{\text{pulm artery}} - P_{\text{L atrium}}}{\text{Cardiac output}}$$

$P_{\text{pulm artery}}$  = pressure in pulmonary artery

Note:  $P_{\text{L atrium}}$  = pulmonary wedge pressure

Remember:  $\Delta P = Q \times R$ , so  $R = \Delta P / Q$

**Oxygen content of blood**

$\text{O}_2$  content = ( $\text{O}_2$  binding capacity  $\times$  % saturation) + dissolved  $\text{O}_2$ .

Normally 1 g Hgb can bind 1.34 mL  $\text{O}_2$ ; normal Hgb amount in blood is 15 g/dL.

Normal  $\text{O}_2$  binding capacity  $\approx 20.1$  mL  $\text{O}_2$  / dL.

$\text{O}_2$  content of arterial blood  $\downarrow$  as [Hgb] falls, but  $\text{O}_2$  saturation and arterial  $\text{PO}_2$  do not.

Arterial  $\text{PO}_2 \downarrow$  with chronic lung disease; physiologic shunt  $\downarrow$   $\text{O}_2$  extraction ratio

**Alveolar gas equation**

$$PA_{\text{O}_2} = PI_{\text{O}_2} - \frac{PA_{\text{CO}_2}}{R}$$

$PA_{\text{O}_2}$  = alveolar  $\text{PO}_2$  (mm Hg)

$PI_{\text{O}_2}$  =  $\text{PO}_2$  in inspired air (mm Hg)

$PA_{\text{CO}_2}$  = alveolar  $\text{PCO}_2$  (mm Hg)

R = respiratory quotient

A-a gradient =  $PA_{\text{O}_2} - Pa_{\text{O}_2} = 10\text{--}15$  mm Hg

$\uparrow$  A-a gradient may occur in hypoxemia; causes include shunting, high V/Q mismatch, fibrosis (diffusion block)

Can normally be approximated:

$$PA_{\text{O}_2} = 150 - P_{\text{art CO}_2} / 0.8$$

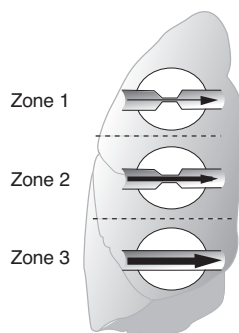
**V/Q mismatch**

Ideally, ventilation is matched to perfusion (i.e.,  $V/Q = 1$ ) in order for adequate gas exchange.

Lung zones:

1. Apex of the lung— $V/Q = 3$  (wasted ventilation)
2. Base of the lung— $V/Q = 0.6$  (wasted perfusion)

Both ventilation and perfusion are greater at the base of the lung than at the apex of the lung.



Apex:  $P_A > P_a > P_v \rightarrow V/Q = 3$   
(wasted ventilation)

$P_a > P_A > P_v$

Base:  $P_a > P_v > P_A \rightarrow V/Q = 0.6$   
(wasted perfusion); NOTE: both ventilation and perfusion are greater at the base of the lung than at the apex

With exercise ( $\uparrow$  cardiac output), there is vasodilation of apical capillaries, resulting in a V/Q ratio that approaches 1.

Certain organisms that thrive in high  $\text{O}_2$  (e.g., TB) flourish in the apex.

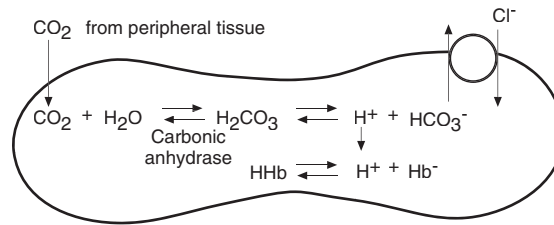
$V/Q \rightarrow 0$  = airway obstruction (shunt).

$V/Q \rightarrow \infty$  = blood flow obstruction (physiologic dead space).

## CO<sub>2</sub> transport

Carbon dioxide is transported from tissues to the lungs in 3 forms:

1. Bicarbonate (90%)



In lungs, oxygenation of hemoglobin promotes dissociation of CO<sub>2</sub> from hemoglobin (Haldane effect).  
In peripheral tissue, ↑ H<sup>+</sup> shifts curve to right, unloading O<sub>2</sub> (Bohr effect).

2. Bound to hemoglobin as carbaminohemoglobin (5%)
3. Dissolved CO<sub>2</sub> (5%)

(Adapted, with permission, from Ganong WF. *Review of Medical Physiology*, 22nd ed. New York: McGraw-Hill, 2005:670.)

## Response to high altitude

1. Acute ↑ in ventilation
2. Chronic ↑ in ventilation
3. ↑ erythropoietin → ↑ hematocrit and hemoglobin (chronic hypoxia)
4. ↑ 2,3-DPG (binds to hemoglobin so that hemoglobin releases more O<sub>2</sub>)
5. Cellular changes (↑ mitochondria)
6. ↑ renal excretion of bicarbonate (e.g., can augment by use of acetazolamide) to compensate for the respiratory alkalosis
7. Chronic hypoxic pulmonary vasoconstriction results in RVH

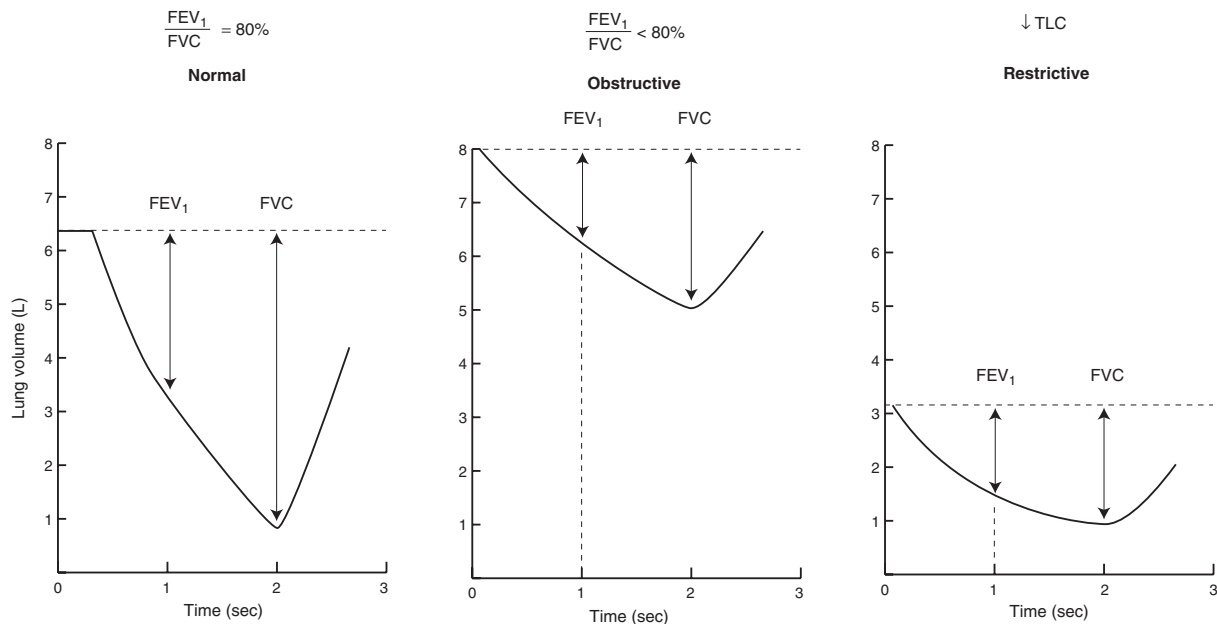


<b>Obstructive lung disease (COPD)</b>		
Obstruction of air flow, resulting in air trapping in the lungs. PFTs: ↓ FEV <sub>1</sub> , ↑ FVC → ↓↓ FEV <sub>1</sub> /FVC ratio (hallmark).		
<b>Type</b>	<b>Pathology</b>	<b>Other</b>
Chronic Bronchitis (“Blue Bloater”)	Hypertrophy of mucus-secreting glands in the bronchioles → Reid index = gland depth / total thickness of bronchial wall; in COPD, Reid index > 50%.	Productive cough for > 3 consecutive months in ≥2 years. Findings: wheezing, crackles, cyanosis.
Emphysema (“pink puffer”)	Enlargement of air spaces and ↓ recoil resulting from destruction of alveolar walls.	↑ elastase activity. Findings: dyspnea, ↓ breath sounds, tachycardia, ↓ I/E ratio. Centriacinar: caused by smoking. Panacinar: α <sub>1</sub> -antitrypsin deficiency (also liver cirrhosis). Paraseptal emphysema: associated with bullae → can rupture → pneumothorax; often in young, otherwise healthy males. Can be triggered by viral URIs, allergens, and stress. Findings: cough, wheezing, dyspnea, tachypnea, hypoxemia, ↓ I/E ratio, pulsus paradoxus, mucus plugging. Associated with bronchial obstruction, CF, poor ciliary motility, Kartagener’s syndrome.
Asthma	Bronchial hyperresponsiveness causes reversible bronchoconstriction. Smooth muscle hypertrophy and Curshmann’s spirals.	
Bronchiectasis	Chronic necrotizing infection of bronchi → permanently dilated airways, purulent sputum, recurrent infections, hemoptysis.	
<hr/>		
<b>Restrictive lung disease</b>		
Restricted lung expansion causes ↓ lung volumes (↓ VC and TLC). PFTs—FEV <sub>1</sub> /FVC ratio > 80%.		
Types:		
<ol style="list-style-type: none"> <li>Poor breathing mechanics (extrapulmonary): <ol style="list-style-type: none"> <li>Poor muscular effort—polio, myasthenia gravis</li> <li>Poor structural apparatus—scoliosis, morbid obesity</li> </ol> </li> <li>Interstitial lung diseases (pulmonary): <ol style="list-style-type: none"> <li>Adult respiratory distress syndrome (ARDS)</li> <li>Neonatal respiratory distress syndrome (hyaline membrane disease)</li> <li>Pneumoconioses (coal miner’s silicosis, asbestosis)</li> <li>Sarcoidosis</li> <li>Idiopathic pulmonary fibrosis</li> <li>Goodpasture’s syndrome</li> <li>Wegener’s granulomatosis</li> <li>Eosinophilic granuloma</li> </ol> </li> </ol>		
<hr/>		
<b>Neonatal respiratory distress syndrome</b>		
Surfactant deficiency leading to ↑ surface tension, resulting in alveolar collapse. Surfactant is made by type II pneumocytes most abundantly after 35th week of gestation. The lecithin-to-sphingomyelin ratio in the amniotic fluid, a measure of lung maturity, is usually < 1.5 in neonatal respiratory distress syndrome. Surfactant—dipalmitoyl phosphatidylcholine. Treatment: maternal steroids before birth; artificial surfactant for infant.		

### Adult acute respiratory distress syndrome (ARDS)

Diffuse alveolar damage → ↑ alveolar capillary permeability → protein-rich leakage into alveoli. Results in formation of intra-alveolar hyaline membrane. Initial damage due to: neutrophilic substances toxic to alveolar wall, activation of coagulation cascade, or oxygen-derived free radicals.

### Obstructive vs. restrictive lung disease



Note: Obstructive lung volumes > normal (↑ TLC, ↑ FRC, ↑ RV); restrictive lung volumes < normal. In both obstructive and restrictive,  $FEV_1$  and FVC are reduced, but in obstructive,  $FEV_1$  is more dramatically reduced, resulting in a ↓  $FEV_1/FVC$  ratio.

### Sleep apnea

Person stops breathing for at least 10 seconds repeatedly during sleep.

**Central sleep apnea**—no respiratory effort.

**Obstructive sleep apnea**—respiratory effort against airway obstruction.

Associated with obesity, loud snoring, systemic/pulmonary hypertension, arrhythmias, and possibly sudden death.

Individuals may become chronically tired.

Treatment: weight loss, CPAP, surgery.

### Asbestosis

Diffuse pulmonary interstitial fibrosis caused by inhaled asbestos fibers. ↑ risk of pleural mesothelioma and bronchogenic carcinoma. Long latency. Ferruginous bodies in lung (asbestos fibers coated with hemosiderin). Ivory-white pleural plaques (see Color Image 42).

Mainly affects lower lobes. Other pneumoconioses affect upper lobes (e.g., coal worker's lung).

Asbestosis and smoking greatly ↑ risk of bronchogenic cancer (smoking not additive with mesothelioma). Seen in shipbuilders and plumbers.

**Lung—physical findings**

Abnormality	Breath Sounds	Resonance	Fremitus	Tracheal Deviation
Bronchial obstruction	Absent/↓ over affected area	↓	↓	Toward side of lesion
Pleural effusion	↓ over effusion	Dullness	↓	—
Pneumonia (lobar)	May have bronchial breath sounds over lesion	Dullness	↑	—
Pneumothorax	↓	Hyperresonant	Absent	Away from side of lesion (see Color Image 40)

**Lung cancer**

Lung cancer is the leading cause of cancer death. Presentation: cough, hemoptysis, bronchial obstruction, wheezing, pneumonic “coin” lesion on x-ray film.

**SPHERE** of complications:

Superior vena cava syndrome  
 Pancoast’s tumor  
 Horner’s syndrome  
 Endocrine (paraneoplastic)  
 Recurrent laryngeal symptoms (hoarseness)  
 Effusions (pleural or pericardial)

Type	Location	Characteristics	Histology
Squamous cell carcinoma (Squamous Central Smoking)	Central	Hilar mass arising from bronchus; Cavitation; Clearly linked to Smoking; parathyroid-like activity → PTHrP (see Color Image 36, Image 118).	Keratin pearls and intercellular bridges.
Adenocarcinoma: Bronchial Bronchoalveolar	Peripheral	Develops in site of prior pulmonary inflammation or injury (most common lung CA in non-smokers). Not linked to smoking.	Both types: Clara cells → type II pneumocytes; multiple densities on x-ray of chest.
Small-cell (oat-cell) carcinoma	Central	Undifferentiated → very aggressive; often associated with ectopic production of ACTH or ADH; may lead to Lambert-Eaton syndrome.	Neoplasm of neuroendocrine Kulchitsky cells → small dark blue cells.
Large cell carcinoma	Peripheral	Highly anaplastic undifferentiated tumor; poor prognosis.	Pleomorphic giant cells with leukocyte fragments in cytoplasm.
Carcinoid tumor	—	Secretes serotonin, can cause carcinoid syndrome (flushing, diarrhea, wheezing, salivation).	—
Metastases	—	Very common. Brain (epilepsy), bone (pathologic fracture), and liver (jaundice, hepatomegaly).	—

**Pancoast’s tumor**

Carcinoma that occurs in apex of lung and may affect cervical sympathetic plexus, causing Horner’s syndrome.

Horner’s syndrome—ptosis, miosis, anhidrosis.

► RESPIRATORY–PATHOLOGY (*continued*)**Pneumonia**

Type	Organism(s)	Characteristics
Lobar	Pneumococcus most frequently	Intra-alveolar exudate → consolidation; may involve entire lung
Bronchopneumonia	<i>S. aureus</i> , <i>H. flu</i> , <i>Klebsiella</i> , <i>S. pyogenes</i>	Acute inflammatory infiltrates from bronchioles into adjacent alveoli; patchy distribution involving ≥ 1 lobes (see Image 116)
Interstitial (atypical) pneumonia	Viruses (RSV, adenoviruses), <i>Mycoplasma</i> , <i>Legionella</i> , <i>Chlamydia</i>	Diffuse patchy inflammation localized to interstitial areas at alveolar walls; distribution involving ≥ 1 lobes (see Image 119)

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<b>Lung abscess</b>	Localized collection of pus within parenchyma, usually resulting from bronchial obstruction (e.g., cancer) or aspiration of gastric contents (especially in patients predisposed to loss of consciousness, e.g., alcoholics or epileptics).	
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<b>Pleural effusions</b>		
Transudate	↓ protein content. Due to CHF, nephrotic syndrome, or hepatic cirrhosis.	
Exudate	↑ protein content, cloudy. Due to malignancy, pneumonia, collagen vascular disease, trauma.	

## ► RESPIRATORY–PHARMACOLOGY

<b>H<sub>1</sub> blockers</b>	Reversible inhibitors of H <sub>1</sub> histamine receptors.
<b>1st generation</b>	Diphenhydramine, dimenhydrinate, chlorpheniramine.
Clinical uses	Allergy, motion sickness, sleep aid.
Toxicity	Sedation, antimuscarinic, anti- $\alpha$ -adrenergic.
<b>2nd generation</b>	Loratadine, fexofenadine, desloratadine.
Clinical uses	Allergy.
Toxicity	Far less sedating than 1st generation.

**Asthma drugs**

Nonspecific  
 $\beta$ -agonists  
 $\beta_2$  agonists

**Isoproterenol**—relaxes bronchial smooth muscle ( $\beta_2$ ).

Adverse effect is tachycardia ( $\beta_1$ ).

**Albuterol**—relaxes bronchial smooth muscle ( $\beta_2$ ).

Use during acute exacerbation.

**Salmeterol**—long-acting agent for prophylaxis.

Adverse effects are tremor and arrhythmia.

Methylxanthines

**Theophylline**—likely causes bronchodilation by inhibiting phosphodiesterase, thereby  $\downarrow$  cAMP hydrolysis. Usage is limited because of narrow therapeutic index (cardiotoxicity, neurotoxicity).

Muscarinic  
antagonists  
Cromolyn

**Ipratropium**—competitive block of muscarinic receptors, preventing bronchoconstriction.

Prevents release of mediators from mast cells. Effective only for the prophylaxis of asthma. Not effective during an acute asthmatic attack. Toxicity is rare.

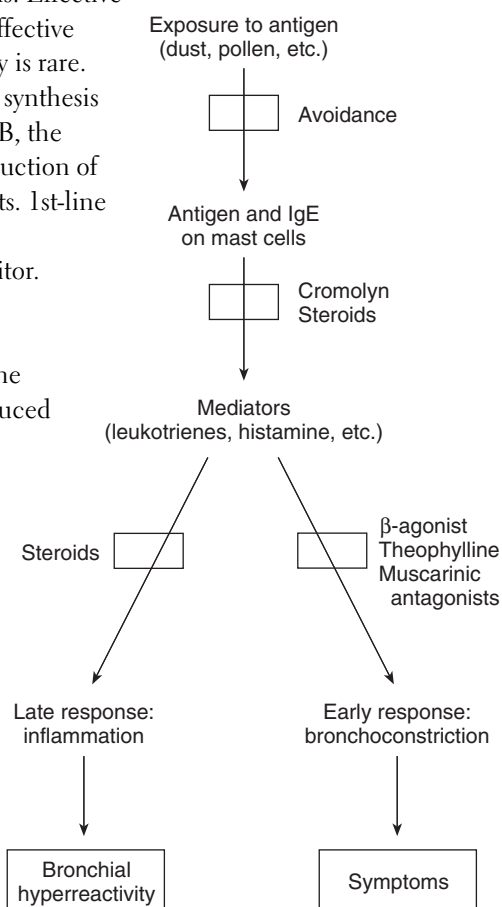
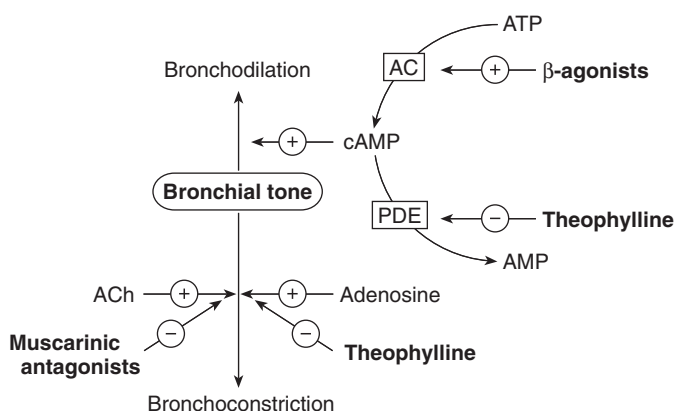
Corticosteroids

**Beclomethasone, prednisone**—inhibit the synthesis of virtually all cytokines. Inactivate NF- $\kappa$ B, the transcription factor that induces the production of TNF- $\alpha$ , among other inflammatory agents. 1st-line therapy for chronic asthma.

Antileukotrienes

**Zileuton**—A 5-lipoxygenase pathway inhibitor. Blocks conversion of arachidonic acid to leukotrienes.

**Zafirlukast, montelukast**—block leukotriene receptors. Especially good for aspirin-induced asthma.



Treatment strategies in asthma

(Adapted, with permission, from Katzung BG, Trevor AJ. *Pharmacology: Examination & Board Review*, 5th ed. Stamford, CT: Appleton & Lange, 1998:159 and 161.)

**Expectorants**

Guaifenesin  
(Robitussin)  
N-acetylcystine

Removes excess sputum but large doses necessary; does not suppress cough reflex.

Mucolytic  $\rightarrow$  can loosen mucus plugs in CF patients.

► CLASSIC FINDINGS

Disease/Finding	Association
Actinic keratosis	Often precedes squamous cell carcinoma
Addison's disease	1° adrenocortical deficiency
Albright's syndrome	Polyostotic fibrous dysplasia, precocious puberty, café-au-lait spots, short stature, young girls
Albuminocytologic dissociation	Guillain-Barré (↑ protein in CSF with only modest ↑ in cell count)
Alport's syndrome	Hereditary nephritis with nerve deafness
Anti-basement membrane antibodies	Goodpasture's syndrome
Anticentromere antibodies	Scleroderma (CREST)
Anti-double-stranded DNA antibodies (ANA antibodies)	SLE (type III hypersensitivity)
Anti-epithelial cell antibodies	Pemphigus vulgaris
Antigliadin antibodies	Celiac disease
Antihistone antibodies	Drug-induced SLE
Anti-IgG antibodies	Rheumatoid arthritis
Antimitochondrial antibodies	1° biliary cirrhosis
Antineutrophil antibodies	Vasculitis
Antiplatelet antibodies	Idiopathic thrombocytopenic purpura
Arachnodactyly	Marfan's syndrome
Argyll Robertson pupil	Neurosyphilis
Arnold-Chiari malformation	Cerebellar tonsillar herniation
Aschoff bodies	Rheumatic fever
Atrophy of the mammillary bodies	Wernicke's encephalopathy
Auer rods	Acute myelogenous leukemia (especially the promyelocytic type)
Autosplenectomy	Sickle cell anemia
Babinski's sign	UMN lesion
Baker's cyst in popliteal fossa	Rheumatoid arthritis
"Bamboo spine" on x-ray	Ankylosing spondylitis
Bartter's syndrome	Hyperreninemia
Basophilic stippling of RBCs	Lead poisoning
Becker's muscular dystrophy	Defective dystrophin; less severe than Duchenne's
Bell's palsy	LMN CN VII palsy
Bence Jones proteins	Multiple myeloma (kappa or lambda Ig light chains in urine), Waldenström's macroglobulinemia (IgM)

Berger's disease	IgA nephropathy
Bernard-Soulier disease	Defect in platelet adhesion
Bilateral hilar adenopathy, uveitis	Sarcoidosis
Birbeck granules on EM	Histiocytosis X (eosinophilic granuloma)
Bloody tap on LP	Subarachnoid hemorrhage
"Blue bloater"	Chronic bronchitis
Blue-domed cysts	Fibrocystic change of the breast
Blue sclera	Osteogenesis imperfecta
Boot-shaped heart on x-ray	Tetralogy of Fallot; RVH
Bouchard's nodes	Osteoarthritis (PIP swelling 2° to osteophytes)
Boutonnière deformity	Rheumatoid arthritis
Branching rods in oral infection	<i>Actinomyces israelii</i>
"Brown tumor" of bone	Hemorrhage causes brown color of osteolytic cysts: 1. Hyperparathyroidism 2. Osteitis fibrosa cystica (von Recklinghausen's disease)
Bruton's disease	X-linked agammaglobulinemia
Budd-Chiari syndrome	Posthepatic venous thrombosis
Buerger's disease	Small/medium-artery vasculitis
Burkitt's lymphoma	8:14 translocation; associated with EBV
Burton's lines	Lead poisoning
C-ANCA, P-ANCA	Wegener's granulomatosis, polyarteritis nodosa
Café-au-lait spots on skin	Neurofibromatosis
Caisson disease	Gas emboli
Calf pseudohypertrophy	Duchenne's muscular dystrophy
Call-Exner bodies	Granulosa-theca cell tumor of the ovary
Cardiomegaly with apical atrophy	Chagas' disease
Cerebriform nuclei	Mycosis fungoides (cutaneous T-cell lymphoma)
Chagas' disease	Trypanosome infection
Chancre	1° syphilis (not painful)
Chancroid	<i>Haemophilus ducreyi</i> (painful)
Charcot's triad	Multiple sclerosis (nystagmus, intention tremor, scanning speech), cholangitis (jaundice, RUQ pain, fever)
Charcot-Leyden crystals	Bronchial asthma (eosinophil membranes)
Chédiak-Higashi disease	Phagocyte deficiency

► CLASSIC FINDINGS (continued)

Cherry-red spot on macula	Tay-Sachs, Niemann-Pick disease, central retinal artery occlusion
Cheyne-Stokes respirations	Central apnea in CHF and ↑ intracranial pressure
“Chocolate cysts”	Endometriosis (frequently involves both ovaries)
Chronic atrophic gastritis	Predisposition to gastric carcinoma
Chvostek’s sign	Hypocalcemia (facial muscle spasm upon tapping)
Clear cell adenocarcinoma of the vagina	DES exposure in utero
Clue cells	<i>Gardnerella vaginitis</i>
Codman’s triangle on x-ray	Osteosarcoma
Cold agglutinins	<i>Mycoplasma pneumoniae</i> , infectious mononucleosis
Cold intolerance	Hypothyroidism
Condylomata lata	2° syphilis
Continuous machinery murmur	Patent ductus arteriosus
Cori’s disease	Debranching enzyme deficiency
Cotton-wool spots	Chronic hypertension
Cough, conjunctivitis, coryza + fever	Measles
Councilman bodies	Toxic or viral hepatitis
Cowdry type A bodies	Herpesvirus
Crescents in Bowman’s capsule	Rapidly progressive crescentic glomerulonephritis
Crigler-Najjar syndrome	Congenital unconjugated hyperbilirubinemia
Curling’s ulcer	Acute gastric ulcer associated with severe burns
Currant-jelly sputum	<i>Klebsiella</i>
Curschmann’s spirals	Bronchial asthma (whorled mucous plugs)
Cushing’s ulcer	Acute gastric ulcer associated with CNS injury
D-dimers	DIC
Depigmentation of neurons in substantia nigra	Parkinson’s disease (basal ganglia disorder—rigidity, resting tremor, bradykinesia)
Dermatitis, dementia, diarrhea	Pellagra (niacin, vitamin B <sub>3</sub> deficiency)
Diabetes insipidus + exophthalmos + lesions of skull	Hand-Schüller-Christian disease
Dog or cat bite	<i>Pasteurella multocida</i>
Donovan bodies	Granuloma inguinale
Dressler’s syndrome	Post-MI fibrinous pericarditis



Dubin-Johnson syndrome	Congenital conjugated hyperbilirubinemia (black liver)
Duchenne's muscular dystrophy	Deleted dystrophin gene (X-linked recessive)
Eburnation	Osteoarthritis (polished, ivory-like appearance of bone)
Edwards' syndrome	Trisomy 18 associated with rocker-bottom feet, low-set ears, heart disease
Eisenmenger's complex	Late cyanosis shunt (uncorrected L → R shunt becomes R → L shunt)
Elastic skin	Ehlers-Danlos syndrome
Erb-Duchenne palsy	Superior trunk brachial plexus injury ("waiter's tip")
Erythema chronicum migrans	Lyme disease
Fanconi's syndrome	Proximal tubular reabsorption defect
"Fat, female, forty, and fertile"	Acute cholecystitis
Fatty liver	Alcoholism
Ferruginous bodies	Asbestosis
Gardner's syndrome	Colon polyps with osteomas and soft tissue tumors
Gaucher's disease	Glucocerebrosidase deficiency
Ghon focus	1° TB
Gilbert's syndrome	Benign congenital unconjugated hyperbilirubinemia
Glanzmann's thrombasthenia	Defect in platelet aggregation
Goodpasture's syndrome	Autoantibodies against alveolar and glomerular basement membrane proteins
Gowers' maneuver	Duchenne's (use of patient's arms to help legs pick self off the floor)
Guillain-Barré syndrome	Idiopathic polyneuritis
"Hair-on-end" appearance on x-ray	β-thalassemia, sickle cell anemia (extramedullary hematopoiesis)
Hand-Schüller-Christian disease	Chronic progressive histiocytosis
HbF	Thalassemia major
HbS	Sickle cell anemia
hCG elevated	Choriocarcinoma, hydatidiform mole (occurs with and without embryo)
Heberden's nodes	Osteoarthritis (DIP swelling 2° to osteophytes)
Heinz bodies	G6PD deficiency
Henoch-Schönlein purpura	Hypersensitivity vasculitis associated with hemorrhagic urticaria and URIs
Heterophil antibodies	Infectious mononucleosis (EBV)
High-output cardiac failure (dilated cardiomyopathy)	Wet beriberi (thiamine, vitamin B <sub>1</sub> deficiency)
HLA-B27	Reiter's syndrome, ankylosing spondylitis
HLA-DR3 or -DR4	Diabetes mellitus type 1 (caused by autoimmune destruction of β cells)
Homer Wright rosettes	Neuroblastoma
Honeycomb lung on x-ray	Interstitial fibrosis

► CLASSIC FINDINGS (*continued*)

Horner's syndrome	Ptosis, miosis, and anhidrosis
Howell-Jolly bodies	Splenectomy (or nonfunctional spleen)
Huntington's disease	Caudate degeneration (autosomal dominant)
Hyperphagia + hypersexuality + hyperorality + hyperdocility	Klüver-Bucy syndrome (amygdala)
Hyperpigmentation of skin	1° adrenal insufficiency (Addison's disease)
Hypersegmented neutrophils	Macrocytic anemia
Hypertension + hypokalemia	Conn's syndrome
Hypochromic microcytosis	Iron deficiency anemia, lead poisoning
Increased $\alpha$ -fetoprotein in amniotic fluid/maternal serum	Anencephaly, spina bifida (neural tube defects)
Increased uric acid levels	Gout, Lesch-Nyhan syndrome, myeloproliferative disorders, loop and thiazide diuretics
Intussusception	Adenovirus (causes hyperplasia of Peyer's patches)
Janeway lesions	Endocarditis
Jarisch-Herxheimer reaction	Syphilis—overaggressive treatment of an asymptomatic patient that causes symptoms due to rapid lysis
Job's syndrome	Neutrophil chemotaxis abnormality
Kaposi's sarcoma	AIDS in MSM (men who have sex with men)
Kartagener's syndrome	Dynein defect
Kayser-Fleischer rings	Wilson's disease
Keratin pearls	Squamous cell carcinoma
Kimmelstiel-Wilson nodules	Diabetic nephropathy
Klüver-Bucy syndrome	Bilateral amygdala lesions
Koilocytes	HPV
Koplik spots	Measles
Krukenberg tumor	Gastric adenocarcinoma with ovarian metastases
Kussmaul hyperpnea	Diabetic ketoacidosis
Lens dislocation + aortic dissection + joint hyperflexibility	Marfan's syndrome (fibrillin deficit)
Lesch-Nyhan syndrome	HGPRT deficiency
Lewy bodies	Parkinson's disease
Libman-Sacks disease	Endocarditis associated with SLE
Lines of Zahn	Arterial thrombus
Lisch nodules	Neurofibromatosis (von Recklinghausen's disease)

Low serum ceruloplasmin	Wilson's disease
Lucid interval	Epidural hematoma
"Lumpy-bumpy" appearance of glomeruli on immunofluorescence	Poststreptococcal glomerulonephritis
Lytic bone lesions on x-ray	Multiple myeloma
Mallory bodies	Alcoholic liver disease
Mallory-Weiss syndrome	Esophagogastric lacerations
McArdle's disease	Muscle phosphorylase deficiency
McBurney's sign	Appendicitis
MLF syndrome (INO)	Multiple sclerosis
Monoclonal antibody spike	Multiple myeloma (called the M protein; usually IgG or IgA), MGUS (monoclonal gammopathy of undetermined significance), Waldenström's (M protein = IgM) macroglobulinemia
Myxedema	Hypothyroidism
Necrotizing vasculitis (lungs) and necrotizing glomerulonephritis	Wegener's and Goodpasture's (hemoptysis and glomerular disease)
Needle-shaped, negatively birefringent crystals	Gout
Negri bodies	Rabies
Nephritis + cataracts + hearing loss	Alport's syndrome
Neurofibrillary tangles	Alzheimer's disease
Niemann-Pick disease	Sphingomyelinase deficiency
No lactation postpartum	Sheehan's syndrome (pituitary infarction)
Nutmeg liver	CHF
Occupational exposure to asbestos	Malignant mesothelioma
"Orphan Annie" nuclei	Papillary carcinoma of the thyroid
Osler's nodes	Endocarditis
Owl's eye	CMV
Painless jaundice	Pancreatic cancer (head)
Palpable purpura on legs and buttocks	Henoch-Schönlein purpura
Pancoast's tumor	Bronchogenic apical tumor associated with Horner's syndrome
Pannus	Rheumatoid arthritis
Parkinson's disease	Nigrostriatal dopamine depletion
Periosteal elevation on x-ray	Pyogenic osteomyelitis
Peutz-Jeghers syndrome	Benign polyposis
Peyronie's disease	Penile fibrosis

► CLASSIC FINDINGS (continued)

Philadelphia chromosome ( <i>bcr-abl</i> )	CML (may sometimes be associated with AML)
Pick bodies	Pick's disease
Pick's disease	Progressive dementia, similar to Alzheimer's
"Pink puffer"	Emphysema (centroacinar [smoking], panacinar [ $\alpha_1$ -antitrypsin deficiency])
Plummer-Vinson syndrome	Esophageal webs with iron deficiency anemia
Podagra	Gout (MP joint of hallux)
Podocyte fusion	Minimal change disease
Polyneuropathy, cardiac pathology, and edema	Dry beriberi (thiamine, vitamin B <sub>1</sub> deficiency)
Polyneuropathy preceded by GI or respiratory infection	Guillain-Barré syndrome
Pompe's disease	Lysosomal glucosidase deficiency associated with cardiomegaly
Port-wine stain	Hemangioma
Positive anterior "drawer sign"	Anterior cruciate ligament injury
Pott's disease	Vertebral tuberculosis
Pseudopalisade tumor cell arrangement	Glioblastoma multiforme
Pseudorosettes	Ewing's sarcoma
Ptosis, miosis, anhidrosis	Horner's syndrome (Pancoast's tumor)
Rash on palms and soles	2° syphilis, Rocky Mountain spotted fever
Raynaud's syndrome	Recurrent vasospasm in extremities
RBC casts in urine	Acute glomerulonephritis
Recurrent pulmonary <i>Pseudomonas</i> and <i>S. aureus</i> infections	Cystic fibrosis
Red urine in the morning	Paroxysmal nocturnal hemoglobinuria
Reed-Sternberg cells	Hodgkin's lymphoma
Reid index (increased)	Chronic bronchitis
Reinke crystals	Leydig cell tumor
Reiter's syndrome	Urethritis, conjunctivitis, arthritis
Renal cell carcinoma + cavernous hemangiomas + adenomas	von Hippel-Lindau disease
Renal epithelial casts in urine	Acute toxic/viral nephrosis
Rhomboid crystals, positively birefringent	Pseudogout

Rib notching	Coarctation of aorta
Roth's spots in retina	Endocarditis
Rotor's syndrome	Congenital conjugated hyperbilirubinemia
Rouleaux formation (RBCs)	Multiple myeloma
Russell bodies	Multiple myeloma
S3	Left-to-right shunt (VSD, PDA, ASD), mitral regurgitation, LV failure (CHF)
S4	Aortic stenosis, hypertrophic subaortic stenosis
Schiller-Duval bodies	Yolk sac tumor
Senile plaques	Alzheimer's disease
Sézary syndrome	Cutaneous T-cell lymphoma
Sheehan's syndrome	Postpartum pituitary necrosis
Shwartzman reaction	<i>Neisseria meningitidis</i>
Signet-ring cells	Gastric carcinoma
Simian crease	Down syndrome
Sipple's syndrome	MEN type IIa
Sjögren's syndrome	Dry eyes, dry mouth, arthritis
Skip lesions	Crohn's
Slapped cheeks	Erythema infectiosum (fifth disease)
Smith antigen	SLE
"Smudge cell"	CLL
Soap bubble on x-ray	Giant cell tumor of bone
Spike and dome on EM	Membranous glomerulonephritis
Spitz nevus	Benign juvenile melanoma
Splinter hemorrhages in fingernails	Endocarditis
Starry-sky pattern	Burkitt's lymphoma
"Strawberry tongue"	Scarlet fever
Streaky ovaries	Turner's syndrome
String sign on x-ray	Crohn's disease
Subepithelial humps on EM	Poststreptococcal glomerulonephritis
Suboccipital lymphadenopathy	Rubella
Sulfur granules	<i>Actinomyces israelii</i>
Swollen gums, bruising, poor wound healing, anemia	Scurvy (ascorbic acid, vitamin C deficiency)—vitamin C is necessary for hydroxylation of proline and lysine in collagen synthesis
Systolic ejection murmur (crescendo-decrescendo)	Aortic valve stenosis

► CLASSIC FINDINGS (*continued*)

t(8;14)	Burkitt's lymphoma ( <i>c-myc</i> activation)
t(9;22)	Philadelphia chromosome, CML ( <i>bcr-abl</i> hybrid)
t(14;18)	Follicular lymphomas ( <i>bcl-2</i> activation)
Tabes dorsalis	3° syphilis
Tendon xanthomas (classically Achilles)	Familial hypercholesterolemia
Thumb sign on lateral x-ray	Epiglottitis ( <i>Haemophilus influenzae</i> )
Thyroidization of kidney	Chronic bacterial pyelonephritis
Tophi	Gout
"Tram-track" appearance on LM	Membranoproliferative glomerulonephritis
Trousseau's sign	Visceral cancer, pancreatic adenocarcinoma (migratory thrombophlebitis), hypocalcemia (carpal spasm)
Virchow's node	Left supraclavicular node enlargement from metastatic carcinoma of the stomach
Virchow's triad	Pulmonary embolism (triad = blood stasis, endothelial damage, hypercoagulation)
von Recklinghausen's disease	Neurofibromatosis with café-au-lait spots
von Recklinghausen's disease of bone	Osteitis fibrosa cystica ("brown tumor")
Wallenberg's syndrome	PICA thrombosis
Waterhouse-Friderichsen syndrome	Adrenal hemorrhage associated with meningococemia
Waxy casts	Chronic end-stage renal disease
WBC casts in urine	Acute pyelonephritis
WBCs in urine	Acute cystitis
Wermer's syndrome	MEN type I
Whipple's disease	Malabsorption syndrome caused by <i>Tropheryma whippelii</i>
Wilson's disease	Hepatolenticular degeneration
"Wire loop" appearance on LM	Lupus nephropathy
"Worst headache of my life"	Berry aneurysm—associated with adult polycystic kidney disease
Xanthochromia (CSF)	Subarachnoid hemorrhage
Xerostomia + arthritis + keratoconjunctivitis sicca	Sjögren's syndrome
Zenker's diverticulum	Upper GI diverticulum
Zollinger-Ellison syndrome	Gastrin-secreting tumor associated with ulcers

## MOST COMMON ASSOCIATIONS

Most Common ...	
Bacteremia/pneumonia (IVDA)	<i>S. aureus</i>
Bacteria associated with cancer	<i>H. pylori</i>
Bacteria found in GI tract	<i>Bacteroides</i> (second most common is <i>E. coli</i> )
Brain tumor (adults)	Mets > astrocytoma (including glioblastoma multiforme) > meningioma > schwannoma
Brain tumor (kids)	Medulloblastoma (cerebellum)
Brain tumor—supratentorial (kids)	Craniopharyngioma
Breast cancer	Infiltrating ductal carcinoma (in the United States, 1 in 9 women will develop breast cancer)
Breast mass	Fibrocystic change (in postmenopausal women, carcinoma is the most common)
Breast tumor (benign)	Fibroadenoma
Bug in debilitated, hospitalized pneumonia patient	<i>Klebsiella</i>
Cardiac 1° tumor (adults)	Myxoma (4:1 left to right atrium; “ball and valve”)
Cardiac 1° tumor (kids)	Rhabdomyoma
Cardiac tumor (adults)	Mets
Cardiomyopathy	Dilated cardiomyopathy
Chromosomal disorder	Down syndrome (associated with ALL, Alzheimer’s dementia, and endocardial cushion defects)
Chronic arrhythmia	Atrial fibrillation (associated with high risk of emboli)
Congenital cardiac anomaly	VSD
Constrictive pericarditis	Tuberculosis
Coronary artery involved in thrombosis	LAD > RCA > LCA
Cyanosis (early; less common)	Tetralogy of Fallot, transposition of great vessels, truncus arteriosus
Cyanosis (late; more common)	VSD, ASD, PDA (close with indomethacin; open with misoprostol)
Demyelinating disease	Multiple sclerosis
Dietary deficit	Iron
Epiglottitis	<i>Haemophilus influenzae</i> type B
Esophageal cancer	Squamous cell carcinoma
Gene involved in cancer	p53 tumor suppressor gene
Group affected by cystic fibrosis	Caucasians (fat-soluble vitamin deficiencies, mucous plugs/lung infections)
Gynecologic malignancy	Endometrial carcinoma
Heart murmur	Mitral valve prolapse

► MOST COMMON ASSOCIATIONS (*continued*)

Heart valve in bacterial endocarditis	Mitral
Heart valve in bacterial endocarditis in IVDA	Tricuspid
Heart valve (rheumatic fever)	Mitral valve (aortic is 2nd)
Helminth infection (U.S.)	<i>Enterobius vermicularis</i> ( <i>Ascaris lumbricoides</i> is 2nd most common)
Hereditary bleeding disorder	von Willebrand's
Kidney stones	Calcium = radiopaque (2nd most common is ammonium = radiopaque; formed by urease-positive organisms such as <i>Proteus vulgaris</i> or <i>Staphylococcus</i> )
Liver disease	Alcoholic liver disease
Location of brain tumors (adults)	Supratentorial
Location of brain tumors (kids)	Infratentorial
Lysosomal storage disease	Gaucher's disease
Male cancer	Prostatic carcinoma
Malignancy associated with noninfectious fever	Hodgkin's disease
Malignant skin tumor	Basal cell carcinoma (rarely metastasizes)
Mets to bone	Breast, lung, thyroid, testes, prostate, kidney
Mets to brain	Lung, breast, skin (melanoma), kidney (renal cell carcinoma), GI
Mets to liver	Colon, gastric, pancreatic, breast, and lung carcinomas
Motor neuron disease	ALS
Neoplasm (kids)	ALL (2nd most common is cerebellar medulloblastoma)
Nephrotic syndrome	Membranous glomerulonephritis
Obstruction of male urinary tract	BPH
Opportunistic infection in AIDS	<i>Pneumocystis carinii</i> pneumonia
Organ receiving mets	Adrenal glands (due to rich blood supply)
Organ sending mets	Lung > breast, stomach
Ovarian tumor (benign)	Serous cystadenoma
Ovarian tumor (malignant)	Serous cystadenocarcinoma
Pancreatic tumor	Adenocarcinoma (head of pancreas)
Patient with ALL/CLL/AML/CML	ALL—child, CLL—adult > 60, AML—adult > 60, CML—adult 35–50
Patient with Hodgkin's	Young male (except nodular sclerosis type—female)
Patient with minimal change disease	Young child
Patient with Reiter's	Male
Pituitary tumor	Prolactinoma (2nd—somatotrophic "acidophilic" adenoma)



Preventable cancer	Lung cancer
Primary bone tumor (adults)	Multiple myeloma
Primary hyperparathyroidism	Adenomas (followed by hyperplasia, then carcinoma)
Primary liver tumor	Hepatoma
Renal tumor	Renal cell carcinoma—associated with von Hippel–Lindau and acquired polycystic kidney disease; paraneoplastic syndromes (erythropoietin, renin, PTH, ACTH)
Secondary hyperparathyroidism	Hypocalcemia of chronic renal failure
Sexually transmitted disease	<i>Chlamydia</i>
Site of diverticula	Sigmoid colon
Site of metastasis	Regional lymph nodes
Site of metastasis (2nd most common)	Liver
Sites of atherosclerosis	Abdominal aorta > coronary > popliteal > carotid
Skin cancer	Basal cell carcinoma
Stomach cancer	Adenocarcinoma
Testicular tumor	Seminoma
Thyroid cancer	Papillary carcinoma
Tracheoesophageal fistula	Lower esophagus joins trachea/upper esophagus—blind pouch
Tumor in men	Prostate carcinoma
Tumor in women	Leiomyoma (estrogen dependent)
Tumor of infancy	Hemangioma
Tumor of the adrenal medulla (adults)	Pheochromocytoma (benign)
Tumor of the adrenal medulla (kids)	Neuroblastoma (malignant)
Type of Hodgkin's	Nodular sclerosis (vs. mixed cellularity, lymphocytic predominance, lymphocytic depletion)
Type of non-Hodgkin's	Follicular, small cleaved
Type of pituitary adenoma	Prolactinoma
Vasculitis	Temporal arteritis (risk of ipsilateral blindness due to thrombosis of ophthalmic artery)
Viral encephalitis	HSV
Vitamin deficiency (U.S.)	Folic acid (pregnant women are at high risk; body stores only 3- to 4-month supply)

► MOST COMMON ASSOCIATIONS (continued)

Most Frequent Cause of ...	
Addison's	Autoimmune (infection is the 2nd most common cause)
Aneurysm, dissecting	Hypertension
Aortic aneurysm, abdominal and descending aorta	Atherosclerosis
Aortic aneurysm, ascending	3° syphilis
Bacterial meningitis (adults)	<i>Neisseria meningitidis</i>
Bacterial meningitis (elderly)	<i>Streptococcus pneumoniae</i>
Bacterial meningitis (kids)	<i>Haemophilus influenzae</i> type B
Bacterial meningitis (newborns)	<i>E. coli</i>
Cancer associated with AIDS	Kaposi's sarcoma
Congenital adrenal hyperplasia	21-hydroxylase deficiency
Cretinism	Iodine deficit/hypothyroidism
Cushing's syndrome	Corticosteroid therapy (2nd most common cause is excess ACTH secretion by pituitary)
Death in CML	Blast crisis
Death in SLE	Lupus nephropathy
Dementia	Alzheimer's (2nd most common is multi-infarct)
DIC	Gram-negative sepsis, obstetric complications, cancer, burn trauma
Ejection click	Aortic/pulmonic stenosis
Food poisoning	<i>S. aureus</i>
Glomerulonephritis (adults)	IgA nephropathy (Berger's disease)
Hematoma—epidural	Rupture of middle meningeal artery (arterial bleeding is fast)
Hematoma—subdural	Rupture of bridging veins (trauma; venous bleeding is slow)
Hemochromatosis	Multiple blood transfusions (can result in CHF and ↑ risk of hepatocellular carcinoma)
Hepatic cirrhosis	EtOH
Hepatocellular carcinoma	Cirrhotic liver (often associated with hepatitis B and C)
Holosystolic murmur	VSD, tricuspid regurgitation, mitral regurgitation
Hypertension, 2°	Renal disease
Hypoparathyroidism	Thyroidectomy
Hypopituitarism	Adenoma
Infection in blood transfusion	Hepatitis C
Infection in burn victims	<i>Pseudomonas</i>

Leukemia (adults)	AML
"Machine-like" murmur	PDA
Mental retardation	Down syndrome (fragile X is the second most common cause)
MI	Atherosclerosis
Mitral valve stenosis	Rheumatic heart disease
Myocarditis	Coxsackie B
Nephrotic syndrome (adults)	Membranous glomerulonephritis
Nephrotic syndrome (kids)	Minimal change disease (associated with infections/vaccinations; treat with corticosteroids)
Opening snap	Mitral stenosis
Osteomyelitis	<i>S. aureus</i>
Osteomyelitis in patients with sickle cell disease	<i>Salmonella</i>
Osteomyelitis with IVDA	<i>Pseudomonas</i>
Pancreatitis (acute)	EtOH and gallstones
Pancreatitis (chronic)	EtOH (adults), cystic fibrosis (kids)
Peau d'orange	Carcinoma of the breast
PID	<i>Neisseria gonorrhoeae</i> (monoarticular arthritis)
Pneumonia, hospital-acquired	<i>Klebsiella</i>
Pneumonia in cystic fibrosis, burn infection	<i>Pseudomonas aeruginosa</i>
Preventable blindness	<i>Chlamydia</i>
Primary amenorrhea	Turner's (XO)
Primary hyperaldosteronism	Adenoma of adrenal cortex
Primary hyperparathyroidism	Adenoma
Pulmonary hypertension	COPD
Right heart failure due to a pulmonary cause	Cor pulmonale
Right-sided heart failure	Left-sided heart failure
Sheehan's syndrome	Postpartum pituitary infarction 2° to hemorrhage
SIADH	Small cell carcinoma of the lung
UTI	<i>E. coli</i>
UTI (young women)	<i>E. coli</i> and <i>Staphylococcus saprophyticus</i>

► EQUATION REVIEW

Topic	Equation	Page
Sensitivity	$\text{Sensitivity} = \frac{a}{a + c}$	65
Specificity	$\text{Specificity} = \frac{d}{b + d}$	65
Positive predictive value	$\text{PPV} = \frac{a}{a + b}$	65
Negative predictive value	$\text{NPV} = \frac{d}{c + d}$	65
Relative risk	$\text{RR} = \frac{\left[ \frac{a}{a + b} \right]}{\left[ \frac{c}{c + d} \right]}$	65
Attributable risk	$\text{AR} = \left[ \frac{a}{a + b} \right] - \left[ \frac{c}{c + d} \right]$	65
Hardy-Weinberg equilibrium	$p^2 + 2pq + q^2 = 1$ $p + q = 1$	114
Henderson-Hasselbalch equation	$\text{pH} = \text{pKa} + \log \frac{[\text{HCO}_3^-]}{0.03 \text{ Pco}_2}$	397
Volume of distribution	$V_d = \frac{\text{amount of drug in the body}}{\text{plasma drug concentration}}$	209
Clearance	$\text{CL} = \frac{\text{rate of elimination of drug}}{\text{plasma drug concentration}}$	209
Half-life	$t_{1/2} = \frac{0.7 \times V_d}{\text{CL}}$	209
Loading dose	$\text{LD} = C_p \times \frac{V_d}{F}$	210
Maintenance dose	$\text{MD} = C_p \times \frac{\text{CL}}{F}$	210
Cardiac output	$\text{CO} = \frac{\text{rate of O}_2 \text{ consumption}}{\text{arterial O}_2 \text{ content} - \text{venous O}_2 \text{ content}}$	232
Cardiac output	$\text{CO} = \text{stroke volume} \times \text{heart rate}$	232
Mean arterial pressure	$\text{MAP} = \text{cardiac output} \times \text{total peripheral resistance}$	232
Mean arterial pressure	$\text{MAP} = \frac{1}{3} \text{ systolic} + \frac{2}{3} \text{ diastolic}$	232
Stroke volume	$\text{SV} = \text{end diastolic volume} - \text{end systolic volume}$	232
Ejection fraction	$\text{EF} = \frac{\text{stroke volume}}{\text{end diastolic volume}} \times 100$	233
Resistance	$R = \frac{\text{driving pressure}}{\text{flow}} = \frac{8\eta \text{ (viscosity)} \times \text{length}}{\pi r^4}$	233
Net filtration pressure	$P_{\text{net}} = [(P_c - P_i) - (\pi_c - \pi_i)]$	241

Glomerular filtration rate	$GFR = U_{\text{inulin}} \times \frac{V}{P_{\text{inulin}}} = C_{\text{inulin}}$	392
Glomerular filtration rate	$GFR = K_f [(P_{GC} - P_{BS}) - (\pi_{GC} - \pi_{BS})]$	392
Effective renal plasma flow	$ERPF = U_{PAH} \times \frac{V}{P_{PAH}} = C_{PAH}$	392
Renal blood flow	$RBF = \frac{RPF}{1 - Hct}$	392
Filtration fraction	$FF = \frac{GFR}{RPF}$	393
Free water clearance	$C_{H_2O} = V - C_{osm}$	393
Physiologic dead space	$V_D = V_T \times \frac{(Paco_2 - Peco_2)}{Paco_2}$	427

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- The quality and number of sample questions
- The quality of written answers to sample questions
- The quality and appropriateness of the illustrations (e.g., graphs, diagrams, photographs)
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- The importance of the discipline for the USMLE Step 1 examination

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**A**

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KAPLAN

[www.kaplanmedical.com](http://www.kaplanmedical.com)

Internet-based question bank providing tailored boards-format exams. Test content and performance feedback are organized by organ system and discipline. Questions are similar in style and content to those on the actual exam but had some reliance on “buzz words.” Includes well-written, detailed explanations. Additional Qbanks for physiology and clinical vignettes are available. Excellent but expensive source of practice questions. Compare closely to *USMLERx* and *USMLE Steps 123* below.

**\$199 for 1 month**

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Internet-based question bank using same interface (FRED) as the USMLE. Question length and level of difficulty are similar to the actual exam. Provides many helpful test selection options and detailed performance analysis. Explanations features high-yield facts from *First Aid for the USMLE Step 1* and other pertinent facts commonly found on the Step 1 exam. Overall, an excellent resource for high-yield questions with useful test analysis options. Limited student feedback.

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**A**

**USMLE Steps 123 Step 1 Question Bank**

ELSEVIER

[www.studentconsult.com/usmle](http://www.studentconsult.com/usmle)

Internet-based question bank that can be divided by discipline and subject areas. Has both practice and test modes. Question length, difficulty, and test interface (FRED) are similar to real exam. Concise explanations with links to StudentConsult and FirstConsult content. User can see cumulative results over time and compared to other test takers. Overall, a great source of practice questions especially with various subscription periods available. Limited student feedback.

**\$49–\$599 for 1-week to 12-month subscriptions**

Test/2100 q

**A**

**WebPath: The Internet Pathology Laboratory**

KLATT

<http://www-medlib.med.utah.edu/WebPath/webpath.html>

Features a wealth of outstanding gross and microscopic illustrations, clinical vignette questions, and case studies. Contains many classic, high-quality illustrations. Includes 8 general pathology exams and 11 system-based exams with a total of more than 800 questions. Also includes 170 questions associated with images. Questions reflect current boards format and difficulty level but are typically shorter. A WebPath CD-ROM is available for \$60.00 and features the online Web site plan supplemented with additional illustrations, topics, tutorials, and radiology.

**Free**

Review/1000 q



<b>B<sup>+</sup></b>	<p><b>Digital Anatomist Interactive Atlases</b>  UNIVERSITY OF WASHINGTON  <a href="http://www9.biostr.washington.edu/da.html">www9.biostr.washington.edu/da.html</a></p> <p>A good site containing an interactive neuroanatomy course along with a 3-dimensional atlas of the brain, thorax, and knee. Atlases have computer-generated images along with cadaver dissections. Each atlas also has a useful quiz in which users identify structures in the slide images. An excellent source for reviewing neuro images.</p>	<b>Free</b>	Review
<b>B<sup>+</sup></b>	<p><b>Lippincott's 350-Question Practice Test for USMLE Step 1</b>  LIPPINCOTT WILLIAMS &amp; WILKINS  <a href="http://www.lww.com/medstudent/usmle/">http://www.lww.com/medstudent/usmle/</a></p> <p>Previously Blackwell's Step 1 Online Q&amp;A. A full-length, seven-block, 350-question practice exam in a format similar to that of the real exam. Questions come with explanations related to the selected answer only. The user can bookmark questions and can take the test all at once or by section.</p>	<b>Free</b>	Test/350 q
<b>B<sup>+</sup></b>	<p><b>The Pathology Guy</b>  FRIEDLANDER  <a href="http://www.pathguy.com">www.pathguy.com</a></p> <p>A free Web site containing extensive but poorly organized information on a variety of fundamental concepts in pathology. Excellent collection of high-yield facts in "Ed's Pathology Review for USMLE," which is buried at the end of each pathology topic page. Philosophical and religious digressions can impede a rapid review of the site.</p>	<b>Free</b>	Review
<b>B</b>	<p><b>USMLEasy</b>  MCGRAW-HILL  <a href="http://www.usmleasy.com/">http://www.usmleasy.com/</a></p> <p>Internet-based question bank based on the PreTest series. Requires an online subscription. Some questions are more obscure than those appearing on the actual exam. Users can track questions completed as well as customize tests. Presented in boards format. Useful as a supplemental review after other resources have been exhausted.</p>	<b>\$99 for 1 month;  \$199 for 3 months</b>	Test/2800 q
<b>B</b>	<p><b>The Whole Brain Atlas</b>  JOHNSON  <a href="http://www.med.harvard.edu/AANLIB/home.html">www.med.harvard.edu/AANLIB/home.html</a></p> <p>A collection of high-quality brain MR and CT images with views of normal, aging, and diseased brains (CVA, degenerative, neoplastic, and inflammatory diseases). The interface is technologically impressive but complex. Guided tours and image correlations to cases are especially useful. Although not all of the images are particularly high yield for the boards, this is an excellent introduction to neuroimaging.</p>	<b>Free</b>	Review

**B-****Active Learning Centre****Free**

Test/100 q

**TURCHIN**[www.med.jhu.edu/medcenter/quiz/home.cgi](http://www.med.jhu.edu/medcenter/quiz/home.cgi)

A quiz engine site based on a large database with an extensive list of bugs, drugs, and vaccines. Questions test the basic characteristics of each element in the database in a multiple-choice, matching, or essay format that the user selects. Questions are not boards style but are useful for learning the memory-intensive subjects of microbiology and pharmacology.

**A*****First Aid Cases for the USMLE Step 1*****\$34.95**

Review

LE

McGraw-Hill, 2006, 272 pages, ISBN 0071464107

Cases organized into same sections as *First Aid for the USMLE Step 1*. Provides 9 to 45 cases per general principle or organ system. Each case includes a paragraph-long clinical vignette followed by questions and detailed explanations. Many cases include very board-appropriate images. Overall, a good supplemental USMLE review resource that provides just the right amount of depth. Limited student feedback.

**A-*****Kaplan's USMLE Step 1 Home Study Program*****\$449.00**

Review

KAPLAN

Kaplan, 2006, 1900 pages, ISBN 0X63410105

Includes two general principles review books and two organ system-based review books. Very dense and comprehensive. Useful only if started early, possibly with coursework. Excellent as a reference for studying. Somewhat expensive for the amount of material. Books can be purchased by calling 1-800-KAP-ITEM or visiting [www.kaptest.com](http://www.kaptest.com).

**A-*****medEssentials*****6 months for \$129**

Review

MANLEY

**12 months for \$189**

Kaplan, 2006, 500 pages, ISBN BK5023A

**25 months for \$279**

Comprehensive review book with great tables and figures. Divided into general principles and organ systems. Contains some high-yield color images in the back. Too detailed in some parts. Comes with monthly subscription to online interactive exercises similar to video games of limited value. Limited student feedback.

**A-*****Step-Up: A High-Yield, Systems-Based Review for the USMLE Step 1*****\$38.95**

Review

MEHTA

Lippincott Williams &amp; Wilkins, 2006, 448 pages, ISBN 078178090X

An organ system-based review text useful for integrating the basic sciences covered in Step 1. Composed primarily of outlines, charts, tables, and diagrams. The appendix includes 38 clinical cases and an alphabetical section on pharmacology. Previous edition contains some errors. The organ system format appeals to many students and serves as a good contrast to other review sources. Includes useful "quick hit" facts. Limited feedback on new edition.

<b>B<sup>+</sup></b>	<p><b><i>Underground Clinical Vignettes: Step 1 Bundle</i></b></p> <p><b>BHUSHAN</b>  Lippincott Williams &amp; Wilkins, 2005, 9 volumes  ISBN 1405104082</p> <p>Bundle includes 9 books. Designed for easy quizzing with a group. Case-based vignettes provide a good review supplement. Best if started early with coursework or used in conjunction with another primary review source.</p>	<b>\$159.95</b>	Review
<b>B<sup>+</sup></b>	<p><b><i>USMLE Step 1 Secrets</i></b></p> <p><b>BROWN</b>  Elsevier, 2003, 324 pages, ISBN 1560535709</p> <p>Clarifies difficult concepts in a concise, easy-to-read manner. Complements other boards study material and focus is on understanding preclinical fundamentals rather than rote memorization. Easy-to-read style allows for rapid review during downtime. Good integration of information. The only drawback is its limited breadth.</p>	<b>\$38.95</b>	Review
<b>B<sup>+</sup></b>	<p><b><i>Medical Boards—Step 1 Made Ridiculously Simple</i></b></p> <p><b>CARL</b>  MedMaster, 2003, 353 pages, ISBN 0940780593</p> <p>Quick and easy reading. The table and chart format is organized by subject. Reviews are mixed. Some charts are poorly labeled. Consider as an adjunct. Compare with <i>Crashing the Boards: USMLE Step 1</i>.</p>	<b>\$29.95</b>	Review
<b>B<sup>+</sup></b>	<p><b><i>Blueprints Step 1 Q&amp;A</i></b></p> <p><b>CLEMENT</b>  Lippincott Williams &amp; Wilkins, 2003, 184 pages,  ISBN 140510323X</p> <p>Contains one full-length exam of 350 questions. Written by students. Good for practicing the multistep questions common on the real exam. Questions are at times a bit easier than the USMLE. Good supplemental source for practice questions about high-yield facts.</p>	<b>\$32.95</b>	Test/350 q
<b>B<sup>+</sup></b>	<p><b><i>Appleton and Lange's USMLE Step 1 Outline Review</i></b></p> <p><b>GOLDBERG</b>  McGraw-Hill, 2006, 364 pages, ISBN 0071451919</p> <p>A comprehensive outline review of basic science topics. Includes essential facts, diseases, and disorders. Also offers a bulleted treatment of major abnormal processes by system. Includes black-and-white images of pathology and histology throughout.</p>	<b>\$39.95</b>	Review

<b>B<sup>+</sup></b>	<p><b><i>Rapid Review for USMLE Step 1</i></b>  <b>GOLJAN</b>  Elsevier, 2002, 314 pages + CD-ROM, ISBN 0323008410  Outline format with high-yield marginal notes, figures, and tables that highlight key content. Narrative clinical boxes illustrate clinical relevance. Practice exams provide USMLE-style questions of mixed quality. The CD-ROM includes the questions from the book, but the user cannot omit previously used questions from practice sessions.</p>	<b>\$34.95</b>	Review/1400 q
<b>B<sup>+</sup></b>	<p><b><i>Deja Review: USMLE Step 1</i></b>  <b>NAHEEDY</b>  McGraw-Hill, 2006, 370 pages, ISBN 0071447903  Features questions and answers in a two-column, quiz-yourself format. Divided according to discipline. Includes a section at the end with high-yield clinical vignettes. Has a few mistakes throughout but is still a great last-second review before the exam. Limited student feedback.</p>	<b>\$19.95</b>	Review
<b>B</b>	<p><b><i>Lange Q&amp;A for the USMLE Step 1</i></b>  <b>KING</b>  McGraw-Hill, 2006, 415 pages, ISBN 0071481729  Features seven subject-based tests and three 100-question comprehensive exams. A good buy for the number of questions. Gives exhaustive explanations of right and wrong answers and offers a reasonable, straightforward, question-based review with which to assess your strengths and weaknesses.</p>	<b>\$39.95</b>	Test/1000 q
<b>B</b>	<p><b><i>Gold Standard Prep Set for USMLE Step 1</i></b>  <b>KNOUSE</b>  Gold Standard, 2004  A set of 55 CDs covering USMLE Step 1 material in over 70 hours. Limited but positive feedback on an updated and expanded set of CDs. Used by some students as a way to review while driving, while working out, and during downtime. Contains some inaccuracies. Available only by mail order through the company's Web site, <a href="http://www.boardprep.net">www.boardprep.net</a>.</p>	<b>\$309.00</b>	Review
<b>B</b>	<p><b><i>NMS Review for USMLE Step 1</i></b>  <b>LAZO</b>  Lippincott Williams &amp; Wilkins, 2002, 436 pages + CD-ROM, ISBN 0781732921  A text that includes a CD-ROM and serves as a good source of practice questions and answers. Some questions are too picky or difficult. Annotated explanations are well written but are sometimes unnecessarily detailed. Organized as 17 practice exams. The six pages of color plates are helpful. The CD-ROM attempts to simulate the CBT format but is disorganized.</p>	<b>\$42.95</b>	Test/850 q

**B*****Kaplan's USMLE Step 1 Qbook*****\$44.95**

Test/850 q

**MANLEY**

Kaplan, 2006, 446 pages, ISBN 1419551499

Consists of seventeen 50-question exams organized by the traditional basic science disciplines. Good USMLE-style questions with clear, detailed explanations. Lacks classic images typically seen on the exam. Also includes test-taking strategies guide. Comparable to the Lange and NMS question reviews.

**B*****PreTest Clinical Vignettes for the USMLE Step 1*****\$25.95**

Test/400 q

**MCGRAW-HILL**

McGraw-Hill, 2005, 366 pages, ISBN 0071422919

Clinical vignette-style questions with detailed explanations. Organized as eight blocks of 50 questions covering basic sciences. Serves as a good self-evaluation tool, although questions may not mirror those on the actual exam.

**B*****USMLE Step 1 Recall: Buzzwords for the Boards*****\$36.95**

Review

**REINHEIMER**

Lippincott Williams & Wilkins, 2004, 464 pages,  
ISBN 0781745136

Quizzes on main topics and key points presented in a two-column question-and-answer format. Good for self-testing, group study, and quick review. Use as a change of pace. Hits many important clinical features but is not comprehensive or tightly organized. Sometimes focuses on obscure details and memorization rather than on the comprehension and integration that the USMLE emphasizes.

**B*****USMLE Step 1 Recall PDA: Buzzwords for the Boards*****\$34.95**

PDA

**REINHEIMER**

Lippincott Williams &amp; Wilkins, 2004, ISBN 0781754216

The PDA version of the book of the same name. Useful for quick review.

**B*****PreTest Physical Diagnosis*****\$24.95**

Test/500 q

**RETEGUIZ**

McGraw-Hill, 2003, 382 pages, ISBN 0071411402

A collection of clinical vignettes organized by body system, presented in a style similar to that of other books in the PreTest series. May be beyond the scope of Step 1, but could also be used in the clinical years of medical school. Limited student feedback.

**B*****Cracking the Boards: USMLE Step 1*****\$34.95**

Review/400 q

STEIN

Random House, 2000, 832 pages, ISBN 0375761632

A comprehensive text review based on the USMLE content outline, written by past and present medical students. The style is wordy and broad but offers few details. The organ-based format appeals to some students. Includes many labeled illustrations, charts, and photos.

**B*****Crashing the Boards: USMLE Step 1*****\$29.95**

Review

YEH

Lippincott Williams &amp; Wilkins, 1999, 167 pages, ISBN 0781719771

Brief coverage of high-yield topics. Great diagrams; exhibits a good sense of humor. No photos are included. Good organization (bulleted facts and highlighted boxing); useful for supplementary, last-minute review. Incomplete and outdated book reviews are included in the back. Retains outdated strategies for the paper-and-pencil exam. Compare with *Medical Boards—Step 1 Made Ridiculously Simple*.

**B-*****Exam Master Step 1*****\$149.00**

Test/8000 q

EXAM MASTER

Exam Master Corporation, 2004, ISBN 158129087X

Windows/Mac-based testing software with access to up to 8000 Step 1 questions. Interface and exam set-up can be difficult. Questions can be relatively simple or very obscure. Offers the ability to hide multiple-choice options. The new version eliminates K-type and nonclinical questions and is compatible with Windows 98.

**B-*****Rypins' Basic Sciences Review, Vol. I*****\$42.95**

Review/1000 q

FROLICH

Lippincott Williams &amp; Wilkins, 2001, 832 pages, ISBN 0781725186

A multitopic textbook with few figures and tables. A good general reference, but should be used with other subject-specific sources. Well priced for the number of pages and questions. Requires extensive time commitment. Includes good pathology and pharmacology coverage.

**B-*****Rypins' Questions and Answers for Basic Sciences Review*****\$34.95**

Test/1600 q

FROLICH

Lippincott Williams &amp; Wilkins, 2001, 288 pages + CD-ROM, ISBN 0781725208

Questions with answers to supplement *Rypins' Basic Sciences Review*. A decent overall question-based review of all subjects. Good-quality questions, but answers lack detail. Requires time commitment.

**A-****High-Yield Embryology****\$25.95**

Review

DUDEK

Lippincott Williams &amp; Wilkins, 2001, 151 pages,

ISBN 0781721326

A very good, concise review of embryology for the USMLE. Offers excellent organization with clinical correlations. Includes a high-yield list of embryologic origins of tissues. No index or questions.

**A-****High-Yield Neuroanatomy****\$25.95**

Review

FIX

Lippincott Williams &amp; Wilkins, 2005, 178 pages,

ISBN 0781758998

A clean, easy-to-read outline format. Offers straightforward text with excellent diagrams and illustrations. The first several chapters are particularly good. Compare with *Clinical Neuroanatomy Made Ridiculously Simple*. No index.

**A-****Rapid Review: Gross and Developmental Anatomy****\$31.95**

Review/100 q

MOORE

Elsevier, 2002, 220 pages + CD-ROM, ISBN 0323012019

A detailed treatment of basic anatomy and embryology, presented in an outline format similar to that of other books in the series. At times more detailed than necessary for boards review. Contains high-yield charts and figures throughout. Two 50-question tests with extensive explanations are included, with additional questions on the CD-ROM. Compare to *High-Yield Anatomy*.

**A-****Case Files: Gross Anatomy****\$29.95**

Review

TOY

McGraw-Hill, 2005, 345 pages, ISBN 0071437797

A resource that offers both gross anatomy basics and clinical cases covering several high-yield anatomy topics. Also features a concise discussion of anatomy essentials. Diagrams are sparse but high yield.

**A-****USMLE Road Map: Gross Anatomy****\$25.95**

Review/100 q

WHITE

McGraw-Hill, 2005, 240 pages, ISBN 0071445161

An outline treatment of gross anatomy with clinical correlations throughout. Also features high-yield facts in boldface along with numerous high-yield charts and figures. Clinical problems with explanations are given at the end of each chapter. An especially effective chart format is used throughout, with clearly labeled illustrations of basic anatomy. Good integration of facts.



<b>A<sup>-</sup></b>	<p><b><i>USMLE Road Map: Neuroscience</i></b>  <b>WHITE</b>          McGraw-Hill, 2004, 208 pages, ISBN 0071422870</p> <p>An outline review of basic anatomy and physiology with clinical correlations throughout. Also features high-yield facts in boldface along with numerous high-yield charts and figures. Clinical problems with explanations are given at the end of each chapter.</p>	<b>\$24.95</b>	Review/80 q
<b>B<sup>+</sup></b>	<p><b><i>High-Yield Gross Anatomy</i></b>  <b>DUDEK</b>          Lippincott Williams &amp; Wilkins, 2001, 190 pages, ISBN 0781730430</p> <p>An excellent, concise review with clinical correlations. Contains well-labeled, high-yield radiologic images. May be useful to supplement with an atlas. No index.</p>	<b>\$25.95</b>	Review
<b>B<sup>+</sup></b>	<p><b><i>Clinical Neuroanatomy Made Ridiculously Simple</i></b>  <b>GOLDBERG</b>          MedMaster, 2005, 97 pages + CD-ROM, ISBN 0940780577</p> <p>An easy-to-read, memorable, and simplified format with clever hand-drawn diagrams. Offers a quick, high-yield review of clinical neuroanatomy. Good emphasis on clinically relevant pathways, cranial nerves, and neurologic diseases. Includes a CD-ROM that offers CT and MRI images as well as a tutorial on neurologic localization. Compare with <i>High-Yield Neuroanatomy</i>.</p>	<b>\$19.95</b>	Review/Few q
<b>B</b>	<p><b><i>Neuroscience at a Glance</i></b>  <b>BARKER</b>          Blackwell Science, 2003, 132 pages, ISBN 1405111240</p> <p>A high-yield treatment of basic principles in neuroscience using figures only, with one topic presented on each page. Includes a highly effective appendix of pathways. Most useful when used with the neuroscience course. Limited student feedback.</p>	<b>\$31.95</b>	Review
<b>B</b>	<p><b><i>Underground Clinical Vignettes: Anatomy</i></b>  <b>BHUSHAN</b>          Lippincott Williams &amp; Wilkins, 2005, 148 pages, ISBN 1405104090</p> <p>Concise clinical cases illustrating approximately 100 frequently tested diseases with an anatomic basis. Cardinal signs, symptoms, and buzzwords are highlighted. Use as a supplement to other sources of review.</p>	<b>\$19.95</b>	Review

**B*****Platinum Vignettes: Anatomy and Embryology*****\$25.95**

Review

**BROCHERT**

Elsevier, 2003, 110 pages, ISBN 1560535814

Fifty clinical case scenarios presented in a user-friendly format, with the question appearing on the front of each page and the answer printed on the back. Similar in style to other books in the Platinum Vignettes series; may be of benefit for students who wish to self-quizz. Relatively few cases are presented considering that both anatomy and embryology are covered. Expensive for amount of material.

**B*****Gray's Anatomy Flash Cards*****\$34.95**

Flash cards

**DRAKE**

Elsevier, 2005, 320 pages, ISBN 0443069107

Front of each card has detailed anatomical illustration while the back identifies the structures in the illustration along with giving systematically and clinically relevant information. Include some radiology review cards and clinical question cards that are good for boards review. Comes in a nice box for the cards. Overall, might be too detailed for USMLE studying.

**B*****BRS Embryology*****\$36.95**

Review/500 q

**DUDEK**

Lippincott Williams &amp; Wilkins, 2004, 336 pages, ISBN 0781757266

An outline-based review of embryology that is typical for the BRS series. Offers a good but overly detailed review of important embryology. A discussion of congenital malformations is included at the end of each chapter along with relevant questions. The comprehensive exam at the end of the book is high yield.

**B*****BRS Neuroanatomy*****\$34.95**

Review/500 q

**FIX**

Lippincott Williams &amp; Wilkins, 2002, 457 pages, ISBN 0781728290

An updated text that covers the anatomy and embryology of the nervous system. Complete but too lengthy for USMLE review; requires time commitment. Compare with *High-Yield Neuroanatomy* by the same author.

**B*****Clinical Anatomy Made Ridiculously Simple*****\$19.95**

Review

**GOLDBERG**

MedMaster, 2004, 175 pages, ISBN 0940780534

Easy reading, simple diagrams, and lots of mnemonics and amusing associations. Incomplete. The humorous style has variable appeal to students, so browse before buying. Offers good coverage of selected topics. Best if used during coursework.

<b>B</b>	<p><b>Netter's Clinical Anatomy</b> HANSON Elsevier, 2005, 600 pages, ISBN 192900771X This book includes many of the famous Netter's anatomy and embryology images with short descriptions. It also includes helpful clinical correlation pages for many of the common diseases. Definitely a wonderful anatomy reference text during boards studying, but it is too long and detailed to be used as a primary review source.</p>	<p><b>\$46.95</b>      Review</p>
<b>B</b>	<p><b>PreTest Neuroscience</b> SIEGEL McGraw-Hill, 2005, 322 pages, ISBN 0071436510 Similar to other books in the PreTest series. Features a question-and-answer format that is not necessarily in USMLE style. Black-and-white images are referenced to questions throughout. Includes a brief high-yield section. Limited student feedback.</p>	<p><b>\$25.95</b>      Test/500 q</p>
<b>B</b>	<p><b>BRS Gross Anatomy Flash Cards</b> SWANSON Lippincott Williams &amp; Wilkins, 2005, 254 pages, ISBN 0781756545 High-yield anatomy clinical cases presented in flash-card format. Anatomy basics are generally excluded. A useful, boards-relevant resource for students who like to study with flash cards and are reasonably well versed in anatomy.</p>	<p><b>\$29.95</b>      Flash cards</p>
<b>B</b>	<p><b>Blueprints Notes &amp; Cases: Neuroscience</b> WECHSLER Lippincott Williams &amp; Wilkins, 2003, 240 pages, ISBN 1405103493 High-yield cases followed by a discussion and tables, presented in a format similar to that of other books in the Blueprints series. Offers important gross neuroanatomy and neurophysiology facts, but diagrams must be improved if the book is to be considered sufficiently comprehensive for boards review.</p>	<p><b>\$28.95</b>      Review</p>
<b>B-</b>	<p><b>Anatomy Recall</b> ANTEVIL Lippincott Williams &amp; Wilkins, 2005, 384 pages, ISBN 078179885X Presented in question-and-answer format. Good for quick review, but too detailed for boards review.</p>	<p><b>\$34.95</b>      Review</p>

<b>B-</b>	<p><b><i>BRS Gross Anatomy</i></b>  <b>CHUNG</b>  Lippincott Williams &amp; Wilkins, 2005, 512 pages,  ISBN 0781753090</p> <p>A detailed, lengthy text in outline format with illustrations and tables. Better for coursework than for quick boards review, especially for a lower yield subject. Features a good clinical correlation section.</p>	<b>\$36.95</b>	Review/500 q
<b>B-</b>	<p><b><i>Manter and Gatz's Essentials of Clinical Neuroanatomy and Neurophysiology</i></b>  <b>GILMAN</b>  F. A. Davis, 2002, 281 pages, ISBN 0803607725</p> <p>A well-organized discussion of neuroanatomy, neurophysiology, and neuropharmacology presented with illustrations and images. Too dense for boards review.</p>	<b>\$33.95</b>	Review
<b>B-</b>	<p><b><i>Histology and Neural Anatomy</i></b>  <b>PAPKA</b>  Biotest, Inc., 2004, 427 pages, ISBN 1893720136</p> <p>A comprehensive outline review. Lacks illustrations and includes a large number of low-quality questions with no explanations, but answers are cross-referenced to the text. Consider using with coursework. Limited student feedback.</p>	<b>\$25.95</b>	Review/2000 q
<b>B-</b>	<p><b><i>Clinical Anatomy: An Illustrated Review</i></b>  <b>SNELL</b>  Lippincott Williams &amp; Wilkins, 2003, 294 pages,  ISBN 0781743168</p> <p>A well-organized summary of Snell's major book. Includes excellent diagrams and tables. Questions incorporate radiographs, CT scans, and MRIs. Does not cover neuroanatomy or embryology. Neither the text nor the questions is as clinical as the title implies. Only some answers have explanations, and most are too short.</p>	<b>\$34.95</b>	Review/500 q
<b>B-</b>	<p><b><i>Imaging Atlas of Human Anatomy</i></b>  <b>WEIR</b>  Elsevier, 2003, 224 pages, ISBN 0723432112</p> <p>An atlas of diagnostic images for all major systems, including MRIs, CT scans, and brief explanations of diagnostic methods. Useful primarily as an imaging reference for boards review.</p>	<b>\$47.95</b>	Text

**A*****High-Yield Behavioral Science*****\$25.95**

Review

FADEM

Lippincott Williams & Wilkins, 2001, 144 pages,  
ISBN 0781730848

A clear, concise, quick review of behavioral science. Offers a logical presentation with cramtable charts, graphs, and tables. Features a short but adequate statistics chapter. No index.

**A-*****Underground Clinical Vignettes: Behavioral Science*****\$19.95**

Review/20 q

BHUSHAN

Lippincott Williams & Wilkins, 2005, 136 pages,  
ISBN 1405104104

Concise clinical cases illustrating commonly tested diseases in behavioral science. Cardinal signs, symptoms, and buzzwords are highlighted. Use as a supplement to other review sources. Although the case diagnoses have been moved to the back of the book, the discussion still reveals the answer on the same page. Some cases lack detail. Twenty questions are included in the back.

**A-*****BRS Behavioral Science*****\$34.95**

Review/500 q

FADEM

Lippincott Williams & Wilkins, 2004, 296 pages,  
ISBN 0781757274

An easy-to-read outline format with boldfacing of key terms. Offers good, detailed coverage of high-yield topics. The text is lengthy and gives more information than may be needed for the USMLE. Includes excellent tables and charts as well as a short but complete statistics chapter. Offers great coverage of ethics and patient communication topics. Also features good review questions, including a 100-question comprehensive exam at the end of the book. The font size of the new edition is significantly smaller than that of previous editions.

**A-*****Rapid Review: Behavioral Science*****\$34.95**

Review/500 q

STEVENS

Elsevier, 2003, 352 pages + CD-ROM, ISBN 0323020070

A quick outline format covering basic topics in behavioral science, human development, and biostatistics, presented in a format similar to that of other books in the Rapid Review series. Two 50-question multiple-choice tests are included with explanations. Somewhat more detailed on specific disorders, but not sufficient as a sole biostatistics review. The CD-ROM contains additional questions. Compare with *High-Yield Behavioral Science*. Limited student feedback.

**B<sup>+</sup>*****Behavioral Sciences and Outpatient Medicine  
for the Boards and Wards*****\$19.95**

Review

AYALA

Lippincott Williams & Wilkins, 2001, 100 pages,  
ISBN 0632045787Presented in a clear and informative format similar to that of other  
books in the Boards and Wards series. Covers some low-yield topics.**B<sup>+</sup>*****Platinum Vignettes: Behavioral Science & Biostatistics*****\$25.95**

Review

BROCHERT

Elsevier, 2003, 106 pages, ISBN 1560535768

A series of cases followed by explanations and discussions on the fol-  
lowing page, presented in a format similar to that of other books in the  
Platinum Vignettes series. In contrast to *Underground Clinical Vi-  
gnettes: Behavioral Science*, the Platinum Vignette series includes vi-  
gnettes for biostatistics; however, there are only half as many cases.  
Expensive for the amount of material.**B<sup>+</sup>*****PreTest Behavioral Science*****\$24.95**

Test/500 q

EBERT

McGraw-Hill, 2001, 300 pages, ISBN 0071374701

Contains detailed answers cross-referenced with other resources.  
Good test questions. Requires time commitment. Includes a brief  
high-yield section.**B<sup>+</sup>*****High-Yield Biostatistics*****\$25.95**

Review

GLASER

Lippincott Williams & Wilkins, 2005, 128 pages,  
ISBN 078179644XA well-written text, but some explanations are confusing. Offers exten-  
sive coverage for a low-yield topic. Includes good review questions  
and tables. For the motivated student; not for last-minute cramming.  
Suitable as a course companion. Best used in conjunction with a be-  
havioral science resource.**B<sup>+</sup>*****Blueprints Notes & Cases: Behavioral  
Science and Epidemiology*****\$28.95**

Review/184 q

NEUGROSCHL

Lippincott Williams & Wilkins, 2003, 224 pages,  
ISBN 1405103558A case-oriented approach to behavioral science, presented as part of  
the Blueprints Notes & Cases series. Includes the HPI, a basic science  
review and discussion, key points, and questions. The 8.5" x 11" lay-  
out may feel overwhelming to some, but the font size is conducive to  
easy review. A good way to master the intangibles of behavioral sci-  
ence, but slightly more detailed than warranted for boards review.

<b>B<sup>+</sup></b>	<p><b><i>Deja Review: Behavioral Science</i></b>  <b>STANFORD</b>          McGraw-Hill, 2006, 216 pages, ISBN 0071468684</p> <p>Features questions and answers in a two-column, quiz-yourself format. Similar to Recall series. Provides a sound review in a different format than straight text. Allows a more interactive review of some hard-to-memorize details needed for USMLE behavioral science questions. Limited student feedback.</p>	<b>\$22.95</b>	Review
<b>B</b>	<p><b><i>Kaplan USMLE Medical Ethics</i></b>  <b>FISCHER</b>          Kaplan, 2006, 208 pages, ISBN 1419542095</p> <p>Includes 100 cases, each with a single multiple-choice question afterward with detailed explanations. First part of book is primarily in text format. Discusses guidelines on how the USMLE requires a test-taker to think about ethics and medicolegal questions. Too long for review of a low-yield subject area but 100 cases could be a useful resource.</p>	<b>\$39.00</b>	Review
<b>B</b>	<p><b><i>USMLE Behavioral Science Made Ridiculously Simple</i></b>  <b>SIERLES</b>          MedMaster, 1997, 171 pages, ISBN 0940780348</p> <p>Easy reading, and reasonably high yield for the amount of text. Includes medical sociology; strong on psychopathology with illustrative examples. No biostatistics. Sometimes offers too much detail on low-yield topics.</p>	<b>\$16.95</b>	Review
<b>B<sup>-</sup></b>	<p><b><i>Epidemiology &amp; Biostatistics Secrets</i></b>  <b>NORDNESS</b>          Elsevier, 2005, 272 pages, ISBN 0323034063</p> <p>Presents information in a similar fashion as other Secrets books. Useful resource for a notably hard-to-study topic with case questions and discussion. Comes with Student Consult online access and extras. Too long and in-depth for boards studying but is a useful reference about biostatistics.</p>	<b>\$36.95</b>	Review

**A-**

***Underground Clinical Vignettes: Biochemistry***

**\$19.95**

Review

**BHUSHAN**

Lippincott Williams & Wilkins, 2005, 136 pages,  
ISBN 1405104112

Concise clinical cases illustrating approximately 100 frequently tested diseases with a biochemical basis. Cardinal signs, symptoms, and buzzwords are highlighted. A useful supplement to other sources of review.

**A-**

***Lippincott's Illustrated Reviews: Biochemistry***

**\$46.95**

Review/250 q

**CHAMPE**

Lippincott Williams & Wilkins, 2004, 608 pages,  
ISBN 0781722659

An excellent book that offers good clinical correlations as well as highly effective color diagrams. Offers a comprehensive review of biochemistry, including some low-yield topics. The new edition also includes high-yield chapter summaries and a "big picture" chapter at the end of the book that highlights the most important concepts. Requires time commitment; skim high-yield diagrams to maximize USMLE review. Best used with coursework.

**A-**

***Rapid Review: Biochemistry***

**\$31.95**

Review/500 q

**PELLEY**

Elsevier, 2003, 320 pages + CD-ROM, ISBN 0323008356

A quick outline format covering basic topics in biochemistry, presented in a format similar to that of other books in the Rapid Review series. High-yield disease correlation boxes are useful for review. Excellent tables and high-yield figures are featured throughout. Also includes two 50-question multiple-choice tests with explanations plus a CD-ROM with additional questions. Compare to *High-Yield Biochemistry*.

**B+**

***Deja Review: Biochemistry***

**\$22.95**

Review

**MANZOUL**

McGraw-Hill, 2007, 216 pages, ISBN 0071474633

Features questions and answers in a two-column, quiz-yourself format. Similar to Recall series. Provides a sound review in a different format than straight text. Includes a helpful chapter on molecular biology. Limited student feedback.



**B<sup>+</sup>*****High-Yield Biochemistry*****\$25.95**

Review

**WILCOX**

Lippincott Williams & Wilkins, 2003, 107 pages,  
ISBN 0781743141

A concise and crammable text in outline format with good clinical correlations at the end of each chapter. Features many diagrams and tables. Good as a study supplement.

**B*****Clinical Biochemistry*****\$45.95**

Review

**GAW**

Churchill Livingstone, 2004, 180 pages, ISBN 0443072698

Biochemistry and physiology presented in a clinical framework. Visually pleasing. Focuses on adult medicine; skimpy on inherited disorders, genetics, and molecular biochemistry. Case studies are included throughout, but no standard question-and-answer exercises are given. Best if used during biochemistry course.

**B*****Clinical Biochemistry Made Ridiculously Simple*****\$22.95**

Review

**GOLDBERG**

MedMaster, 2004, 93 + foldout, ISBN 0940780305

A conceptual approach to clinical biochemistry, presented with humor. The casual style does not appeal to all students. Mnemonics tend to be somewhat complicated. Offers a good overview and integration of all metabolic pathways. Includes a 23-page clinical review that is very high yield and crammable. Also contains a unique foldout "road map" of metabolism. For students with a firm biochemistry background.

**B*****PreTest Biochemistry & Genetics*****\$25.95**

Test/500 q

**INGRAM-SMITH**

McGraw-Hill, 2005, 384 pages, ISBN 0071437479

Difficult questions with detailed, referenced explanations. Best for the motivated student who uses it along with a review book. Contains some questions on biochemical disorders and metabolism but no clinical vignettes. Features six pages of high-yield facts focusing on genetically based diseases.

**B****Case Files: Biochemistry****\$29.95**

Review

**Toy**

McGraw-Hill, 2005, 414 pages, ISBN 0071437819

Text is divided into clinical cases followed by clinical correlations, a discussion, and take-home pearls, presented in a format similar to others in the Case Files series. A few questions accompany each case. The black-and-white figures are sometimes too small to read, but the clinical correlations make biochemistry concepts easier to remember. Too lengthy for rapid review; best for students who enjoys problem-based learning.

**B<sup>+</sup>*****High-Yield Cell and Molecular Biology*****\$24.95**

Review

DUDEK

Lippincott Williams & Wilkins, 1999, 128 pages,  
ISBN 0683303597

Cellular and molecular biology presented in an outline format, with good diagrams and clinical correlations. Brief but complete. Includes descriptions of laboratory techniques and genetic disorders. No questions or vignettes.

**B*****Rapid Review: Histology and Cell Biology*****\$32.95**

Review/500 q

BURNS

Elsevier, 2002, 336 pages + CD-ROM, ISBN 0323008348

Similar to other books in the Rapid Review series. Features an outline of basic concepts with numerous charts, but histology images are very limited. Two 50-question multiple-choice tests are presented with explanations. The CD-ROM contains additional questions and pathology images. Compare to *High-Yield Histology*.

**B*****High-Yield Histology*****\$25.95**

Review

DUDEK

Lippincott Williams & Wilkins, 2004, 288 pages,  
ISBN 0781747635

A quick and easy review of a relatively low-yield subject. Tables include some high-yield information. Contains good pictures. The appendix features classic electron micrographs. Too lengthy for USMLE review.

**B*****BRS Cell Biology and Histology*****\$36.95**

Review/500 q

GARTNER

Lippincott Williams & Wilkins, 2003, 390 pages + CD-ROM,  
ISBN 0781733103

An outline format that is useful for looking up cell biology and histology information, presented in a style that is typical of the BRS series. Could be used alone for cell biology review, but not enough histology images to be considered comprehensive. Includes a CD-ROM with questions.

**B*****Wheater's Functional Histology*****\$69.95**

Text

YOUNG

Elsevier, 2006, 448 pages, ISBN 044306850X

A color atlas with pictures of normal histology and accompanying text. Useful as a text for coursework. Skim through the photomicrographs for USMLE review. Image captions provide an excellent source for the review of basic cell biology.

**B*****PreTest Anatomy, Histology, & Cell Biology*****\$25.95**

Test/500 q

KLEIN

McGraw-Hill, 2005, 526 pages, ISBN 0071437495

Difficult questions with detailed answers as well as some illustrations.

Requires extensive time commitment. Includes a high-yield section that highlights clinically relevant relationships and lessons.

**A**

***Clinical Microbiology Made Ridiculously Simple***

**\$25.95**

Review

GLADWIN

MedMaster, 2004, 272 pages, ISBN 0940780496

A very good chart-based review of microbiology that includes clever and humorous mnemonics. The best of this series. The text is easy to read, and an excellent antibiotic review helps for pharmacology as well. The style of the series does not appeal to everyone. Requires a supplemental source for immunology. Excellent if you have limited time or are “burning out.”

**A**

***Rapid Review: Microbiology and Immunology***

**\$34.95**

Review/100 q

ROSENTHAL

Elsevier, 2002, 361 pages + CD-ROM, ISBN 0323008402

Similar to other books in the Rapid Review series. Contains a significant number of excellent tables and figures. Two 50-question tests with extensive explanations complement the topics covered in the review. The CD-ROM contains additional questions, but their format is poor. Overall, one of the best in the Rapid Review series.

**A-**

***Basic Immunology***

**\$59.95**

Review

ABBAS

Elsevier, 2006, 336 pages, ISBN 1416029745

Text includes colorful diagrams, pictures, and tables that students will find useful for quick review. Also offers abundant text as well as a lengthy glossary for those who wish to delve into the topic further. Features online access to the same text.

**A-**

***Underground Clinical Vignettes: Microbiology Vols. I & II***

**\$17.95 ea.**

Review

BHUSHAN

Lippincott Williams & Wilkins

Microbiology, Vol. I: 2005, 112 pages, ISBN 1495194129

Microbiology, Vol. II: 2005, 134 pages, ISBN 1405104139

Concise clinical cases illustrating frequently tested diseases in microbiology and immunology (approximately 100 cases in each volume). Cardinal signs, symptoms, and buzzwords are highlighted. Use as a supplement to other sources of review.

**A-*****Microcards*****\$32.95**

Flash cards

**HARPAVAT**Lippincott Williams & Wilkins, 2002, 380 pages,  
ISBN 0781722004

A very useful resource for students who like to use flash cards for review. Some cards include excellent flow charts of important classes of bacteria or viruses. Most of the other cards include the bacterium or virus, clinical presentation, pathobiology, diagnosis, treatment, and important quick facts. Recommended to use initially through coursework.

**A-*****High-Yield Immunology*****\$25.95**

Review

**JOHNSON**Lippincott Williams & Wilkins, 2005, 112 pages,  
ISBN 0781774691

Presented in a format typical of the High-Yield series. Accurately covers high-yield details within the topic in proportion to board's coverage of immunology. Good for quick review. Numerous improvements to new edition.

**A-*****Medical Microbiology and Immunology: Examination and Board Review*****\$39.95**

Review/654 q

**LEVINSON**

McGraw-Hill, 2004, 644 pages, ISBN 0071431993

Clear, concise writing with excellent diagrams and tables. Includes an excellent immunology section. The "Summary of Medically Important Organisms" is highly crammable. Requires time commitment. Can be detailed and dense; best if started early with the course. Covers all topics, including some that are low yield. Includes good practice questions and a comprehensive exam, but questions have letter answers only. Compare with *Lippincott's Illustrated Reviews: Microbiology*.

**A-*****Review of Medical Microbiology*****\$36.95**

Test/550 q

**MURRAY**

Elsevier, 2005, 176 pages, ISBN 0323033253

USMLE-style questions are divided into bacteriology, virology, mycology, and parasitology. Contains high-quality color images for many questions and detailed answer explanations for each. Questions are very similar to those on the boards and provides a nice review. Supplements Murray's *Medical Microbiology* textbook.

**B<sup>+</sup>*****Deja Review: Microbiology & Immunology*****\$22.95**

Review

CHEN

McGraw-Hill, 2006, 250 pages, ISBN 0071468668

Features questions and answers in a two-column, quiz-yourself format. Similar to Recall series. Provides a sound review in a different format than straight text. Great resource once a primary review of microbiology has already been done. Limited student feedback.

**B<sup>+</sup>*****Concise Medical Immunology*****\$37.95**

Review

DOAN

Lippincott Williams & Wilkins, 2005, 256 pages,  
ISBN 078175741X

A concise text with useful diagrams, illustrations, and tables. Good for students who need extra immunology review or wish to study the subject thoroughly for the boards. End-of-chapter multiple-choice questions help reinforce key concepts.

**B<sup>+</sup>*****Bugcards: The Complete Microbiology Review  
Flash Cards for Class, the Boards, and the Wards*****\$26.50**

Flash cards

LEVINE

BL Publishing, 2004, 150 pages, ISBN 0967165539

High-quality flash cards designed for rapid class and USMLE microbiology review. Cards cover all medically relevant bacteria, viruses, fungi, and parasites and include important buzzwords, mnemonics, and clinical vignettes to aid in recall. Unique “disease process cards” summarize all organisms for a particular disease (e.g., UTI, pneumonia).

**B<sup>+</sup>*****Review of Immunology*****\$31.95**

Test/500 q

LICHTMAN

Elsevier, 2005, 192 pages, ISBN 0721603432

Complements Abbas's *Cellular and Molecular Immunology* and *Basic Immunology* textbooks. Contains 500 USMLE-style questions with full-color illustrations and answers explanations. Good resource for questions for a lower yield area. Limited student feedback.

**B<sup>+</sup>*****Case Studies in Immunology: Clinical Companion*****\$39.95**

Review

ROSEN

Garland Science, 2004, 288 pages, ISBN 0815341024

Originally designed as a clinical companion to Janeway's *Immunobiology*, this text provides an excellent synopsis of the major disorders of immunity in a clinical vignette format. Integrates basic and clinical sciences. Excellent images, illustrations, questions, and discussion.

**B<sup>+</sup>*****Medical Microbiology and Immunology Flashcards*****\$34.95**

Flash cards

**ROSENTHAL**

Elsevier, 2005, 414 pages, ISBN 032303392X

Flash cards covering the most commonly asked-about bugs. Has full-color images of a microscopic view of the bug and its clinical presentation on one side. The other side has relevant bug information with a short case. Well organized information and comes in a nice carrying case. Also comes with Student Consult online access and extras. A little too much emphasize is placed on “trigger words” relating to each bug. Limited student feedback.

**B<sup>+</sup>*****How the Immune System Works*****\$28.95**

Review

**SOMPAYRAC**

Blackwell Science, 2002, 144 pages, ISBN 063204702X

A concise overview of immunology that attempts to simplify complicated concepts. Includes a good general overview for course work, but best used as a companion to other, more detailed resources. Lacks many of the details that are needed for the boards but many students like to use it as an initial refresher to get the “big picture.” Weak in clinical immunology for USMLE.

**B<sup>+</sup>*****BRS Micro Flash Cards*****\$29.95**

Flash cards

**SWANSON**

Lippincott Williams &amp; Wilkins, 2003, 250 pages, ISBN 078174427X

A series of flash cards featuring questions with answers on the reverse side. Useful for students who enjoy an active style of review. Good last-second microbiology review.

**B<sup>+</sup>*****Case Files: Microbiology*****\$29.95**

Review

**TOY**

McGraw-Hill, 2005, 430 pages, ISBN 0071445749

Fifty clinical microbiology cases reviewed in an interactive learning format. Each case is followed by a clinical correlation, a discussion with boldfaced buzzwords, and questions. Cases are useful for boards review, since key ideas can be readily associated with the appropriate clinical scenario.



<b>B<sup>+</sup></b>	<p><b><i>Clinical Microbiology Review</i></b></p> <p>WARINNER</p> <p>Wysteria, 2001, 150 pages, ISBN 0967783933</p> <p>A concise yet comprehensive review in chart format with some clinical correlations. Each page covers a single organism with ample space for adding notes during class. Contains no immunology. Spatial organization, color coding, and bulleting of facts facilitate review. A great cross-reference section groups organisms by general characteristics. Includes color plates of significant microbes. Limited student feedback.</p>	<b>\$36.95</b>	Review
<b>B<sup>+</sup></b>	<p><b><i>Appleton &amp; Lange Outline Review: Microbiology and Immunology</i></b></p> <p>YOTIS</p> <p>McGraw-Hill, 2003, 200 pages, ISBN 0071405666</p> <p>A well-organized approach to the microbiology section of the boards, addressing all areas included in the exam. Lacks detailed treatment of autoimmune disorders, but an excellent resource to use in addition to class notes. A good resource for organization of the material. Its sparse use of images could be a drawback.</p>	<b>\$29.95</b>	Review
<b>B<sup>+</sup></b>	<p><b><i>Appleton &amp; Lange's Review of Microbiology &amp; Immunology</i></b></p> <p>YOTIS</p> <p>McGraw-Hill, 2001, 254 pages, ISBN 0071362657</p> <p>A large number of questions with detailed answers. Inadequate as a primary source, but a good supplement for the motivated student. Well referenced with effective diagrams, figures, and tables. Includes a good immunology section but weak coverage of immune disorders.</p>	<b>\$34.95</b>	Test/1000+ q
<b>B</b>	<p><b><i>Microbiology and Immunology for the Boards and Wards</i></b></p> <p>AYALA</p> <p>Lippincott Williams &amp; Wilkins, 2005, 256 pages, ISBN 1405104686</p> <p>Similar in style to other books in the Boards and Wards series. Includes many high-yield tables and buzzwords. Some parts are too detailed for USMLE review. Limited student feedback.</p>	<b>\$24.95</b>	Review/100 q
<b>B</b>	<p><b><i>Blueprints Notes &amp; Cases: Microbiology and Immunology</i></b></p> <p>GANDHI</p> <p>Lippincott Williams &amp; Wilkins, 2003, 224 pages, ISBN 1405103477</p> <p>Fifty-eight succinct clinical cases covering boards-relevant microbiology and immunology facts. Charts, tables, illustrations, and useful "thumbnails" are included in the discussion section to facilitate rapid synthesis of key concepts. Best used during microbiology coursework. For students proficient in immunology.</p>	<b>\$28.95</b>	Review

**B*****BRS Microbiology and Immunology*****\$34.95**

Review/500 q

JOHNSON

Lippincott Williams & Wilkins, 2001, 302 pages,  
ISBN 0781727707

A concise outline format with good questions and illustrations. The immunology section is especially useful. For the motivated student.

**B*****Instant Notes in Immunology*****\$34.95**

Review/125 q

LYDYARD

Garland Science, 2004, 336 pages, ISBN 1859960391

A comprehensive review of immunology with effective figures throughout. Well organized, but too detailed for boards review. Best used during the course. Questions are not in current USMLE format and do not include explanations. High-yield tables of principal cytokines and selected molecules are included. Limited student feedback.

**B*****Lippincott's Illustrated Reviews: Microbiology*****\$35.95**

Review/Few q

STROHL

Lippincott Williams & Wilkins, 2001, 516 pages,  
ISBN 0397515685A comprehensive, highly illustrated review of microbiology similar in style to Champe's *Lippincott's Illustrated Reviews: Biochemistry*. Includes a 50-page color section with more than 150 clinical and laboratory photographs. Compare with Levinson's *Medical Microbiology and Immunology*.**B-*****Platinum Vignettes: Microbiology*****\$25.95**

Review

BROCHERT

Elsevier, 2003, 114 pages, ISBN 1560535741

Fifty clinical case scenarios presented in a unique format, with the case question appearing on the front of the page and the answer printed on the back. May be useful for students who wish to self-quiz. Expensive for the amount of material.

**B-*****PreTest Microbiology*****\$24.95**

Test/500 q

KETTERING

McGraw-Hill, 2004, 310 pages, ISBN 0071437487

Mixed-quality questions with detailed, sometimes verbose explanations. Useful for additional question-based review in bacteriology and virology, but not high yield. Includes three pages of high-yield facts.

**A**

***BRS Pathology***

SCHNEIDER

Lippincott Williams & Wilkins, 2005, 412 pages,

ISBN 0781760224

An excellent, concise review with appropriate content emphasis. Features outline-format chapters with boldfacing of key facts. Includes good questions with explanations at the end of each chapter and a comprehensive exam at the end of the book. Offers well-organized tables and diagrams as well as some good black-and-white photographs representative of classic pathology that can be correlated with color photographs from an atlas. Also contains a chapter on laboratory testing and “key associations” with each disease. Short on clinical details for vignette questions. Worth the time investment. Most effective if started early and then reviewed during study periods.

**\$36.95**

Review/500 q

**A-**

***Pathophysiology for the Boards and Wards***

AYALA

Lippincott Williams & Wilkins, 2006, 368 pages,

ISBN 1405105100

A system-based outline with a focus on pathology. Well organized with glossy color plates of relevant pathology and excellent, concise tables. The appendix includes a helpful overview of neurology, immunology, “zebras,” syndromes, and pearls. Good integration of USMLE-relevant material from various subject areas.

**\$36.95**

Review/75 q

**A-**

***Lange Flash Cards: Pathology***

BARON

McGraw-Hill, 2004, 280 pages, ISBN 0071436901

Pathology flash cards with information on one disease per card. Includes pathophysiology, clinical manifestations, treatment, and clinical vignette. Most effective when used at the beginning of the second year through Step 1 preparation. A useful resource with which to organize the breadth of pathology topics covered on the USMLE. Limited student feedback.

**\$29.95**

Flash cards

**A<sup>-</sup>*****Underground Clinical Vignettes:  
Pathophysiology Vols. I, II, & III*****\$19.95 ea.** Review

BHUSHAN

Lippincott Williams &amp; Wilkins

Pathophysiology, Vol. I, 2005, 136 pages, ISBN 1405104147

Pathophysiology, Vol. II, 2005, 136 pages, ISBN 1405104155

Pathophysiology, Vol. III, 2005, 136 pages, ISBN 1405104163

Concise clinical cases illustrating approximately 100 frequently tested pathology and physiology cases in each book. Cardinal signs, symptoms, and buzzwords are highlighted. Use as a supplement to other sources of review.

**B<sup>+</sup>*****Pathology Recall*****\$32.95** Review

CHABRA

Lippincott Williams & Wilkins, 2002, 552 pages,  
ISBN 0781734061

A quiz-based text featuring thousands of brief questions. Not in USMLE format. Similar to others in the Recall series. Beyond the scope of Step 1, but an entertaining break from other reviews. Numerous errors throughout the book.

**B<sup>+</sup>*****Deja Review: Pathology*****\$22.95** Review

GALFIONE

McGraw-Hill, 2007, 275 pages, ISBN 0071474951

Features questions and answers in a two-column, quiz-yourself format. Similar to Recall series. Provides a sound review in a different format than straight text. Includes many pathophysiology relationships opposed to just pathology. Limited student feedback.

**B<sup>+</sup>*****Pocket Companion to Robbins Pathologic Basis of Disease*****\$36.95** Review

MITCHELL

Elsevier, 2006, 816 pages, ISBN 0721602657

Good for reviewing associations between keywords and specific diseases. Highly condensed, complete, and easy to understand. Explains most important diseases and pathologic processes. No photographs or illustrations. Useful as a quick reference.

**B<sup>+</sup>*****PreTest Pathophysiology*****\$24.95** Test/500 q

MUFSON

McGraw-Hill, 2004, 480 pages, ISBN 0071434925

Includes 500 questions and answers with detailed explanations. Questions may be more difficult than those on the boards. Features a brief section of high-yield topics.

**B*****Platinum Vignettes: Pathology I & II*****\$25.95 ea.** Review**BROCHERT**

Elsevier

Pathology, Vol. I, 2003, 118 pages, ISBN 1560535695

Pathology, Vol. II, 2003, 104 pages, ISBN 1560535725

A text consisting of vignettes that are very similar in style to those of the Underground Clinical Vignettes series. However, each volume contains 50 cases for a total of 100, whereas the UCVs offer 300 cases split over three volumes. Overall, offers less bang for the buck than the UCVs.

**B*****PreTest Pathology*****\$24.95** Test/500 q**BROWN**

McGraw-Hill, 2004, 577 pages, ISBN 0071436774

Picky, difficult questions with detailed, complete answers. Questions are often obscure or esoteric. Features high-quality black-and-white photographs but no color illustrations. Can be used as a supplement to other review books. For the motivated student. Thirty-five pages of high-yield facts are useful for concept summaries.

**B*****Appleton & Lange's Review of Pathology*****\$34.95** Test/850 q**CATALANO**

McGraw-Hill, 2002, 344 pages, ISBN 0071389954

Short text sections followed by numerous questions with answers. Some useful high-yield tables are included at the beginning of each section. Features good photomicrographs. Covers both general and organ-based pathology. Can be used as a supplement to more detailed texts. A good review when time is short.

**B*****Colour Atlas of Anatomical Pathology*****\$79.95** Review**COOKE**

Elsevier, 2004, 300 pages, ISBN 0443073600

An impressive photographic atlas of gross pathology. Offers easy-to-read, clinically relevant content. Limited student feedback.

**B*****Rapid Review: Pathology*****\$36.95** Review/500 q**GOLJAN**

Elsevier, 2004, 384 pages + CD-ROM, ISBN 0323023932

Similar to other books in the Rapid Review series. Addresses key concepts in pathology in a bulleted outline format with many tables and figures. High-yield marginal notes are useful, but the text can appear cluttered at times. The CD-ROM contains additional questions, but they are not in boards format. Limited student feedback.

**B*****Lange Smart Charts*****\$24.95**

Review

**GROYSMAN**

McGraw-Hill, 2000, 285 pages, ISBN 0838581757

A flip chart of tables with information grouped together for ease of recall. Organized by body system with mnemonics. Best used as a summary reference for fast review.

**B*****Pathophysiology of Heart Disease*****\$36.95**

Text

**LILLY**

Lippincott Williams & Wilkins, 2006, 464 pages,  
ISBN 0781763215

A collaborative project by medical students and faculty at Harvard. Well organized, easy to read, and concise; offers comprehensive coverage of cardiovascular pathophysiology from the medical student's perspective. Serves as an excellent bridge between the basic and clinical sciences. Very good for review of this subject, but does not cover other areas of pathology tested on the boards. May be too detailed for boards review.

**B*****Pathcards*****\$34.95**

Flash cards

**MARCUCCI**

Lippincott Williams & Wilkins, 2003, 553 pages,  
ISBN 0781743990

Presents comprehensive and detailed information in flash card format rather than attempting to condense boards-relevant material into just one fact per disease state. Appropriate to the level of depth with which pathology is tested on the USMLE.

**B*****Pathophysiology of Disease: Introduction to Clinical Medicine*****\$54.95**

Review/Few q

**MCPHEE**

McGraw-Hill, 2005, 784 pages, ISBN 007144159X

An interdisciplinary course text useful for understanding the pathophysiology of clinical symptoms. Effectively integrates the basic sciences with mechanisms of disease. Features great graphs, diagrams, and tables. Most helpful if used during coursework owing to its length. Includes a few non-boards-style questions. The text's clinical emphasis nicely complements *BRS Pathology*.

**B*****Hematology at a Glance*****\$32.95**

Review

**MEHTA**

Blackwell Science, 2006, 128 pages, ISBN 1405126663

Covers common hematologic issues. Includes color illustrations. Presented in a logical sequence that is easy to read. Good for class use.

<b>B</b>	<p><b><i>Renal Pathophysiology: The Essentials</i></b>  <b>ROSE</b>  Lippincott Williams &amp; Wilkins, 1994, 351 pages,  ISBN 0683073540</p> <p>An excellent review with explanations of various disease processes of the kidney. Includes review questions within the text that are intended for comprehension and are not written in boards style. Would serve as a good reference during boards review.</p>	<b>\$36.95</b>	Review
<b>B</b>	<p><b><i>Color Atlas of Pathophysiology</i></b>  <b>SILBERNAGL</b>  Thieme, 2000, 380 pages, ISBN 0865778663</p> <p>A text containing more than 180 high-quality illustrations demonstrating disturbed physiologic processes that lead to dysfunction. Limited student feedback.</p>	<b>\$39.95</b>	Review
<b>B</b>	<p><b><i>BRS Pathology Flash Cards</i></b>  <b>SWANSON</b>  Lippincott Williams &amp; Wilkins, 2002, 250 cards,  ISBN 0781737109</p> <p>A series of 250 pathology flash cards categorized by organ system. Effective when used with the <i>BRS Pathology</i> textbook, but not comprehensive enough when used alone. Most cards have only one high-yield fact.</p>	<b>\$29.95</b>	Flash cards
<b>B-</b>	<p><b><i>Blueprints Notes &amp; Cases-Pathophysiology: Renal, Hematology, and Oncology</i></b>  <b>CAUGHEY</b>  Lippincott Williams &amp; Wilkins, 2003, 208 pages,  ISBN 1405103523</p> <p>This book follows the format of the Blueprints series, in which each case takes the form of a discussion followed by key points and a series of questions. The pathophysiology volumes would be a good companion to organ-based teaching modules, but the material is neither comprehensive enough nor sufficiently concise to be high yield for intensive boards preparation.</p>	<b>\$28.95</b>	Review
<b>B-</b>	<p><b><i>Rypins' Intensive Reviews: Pathology</i></b>  <b>DAMJANOV</b>  Lippincott Williams &amp; Wilkins, 1998, 398 pages,  ISBN 0397515553</p> <p>Typical of this series. Includes a comprehensive exam with answers and explanations. Illustrated with simple diagrams; no photos are included.</p>	<b>\$21.95</b>	Review/220 q

**B-*****Blueprints Notes & Cases—Pathophysiology:  
Pulmonary, Gastrointestinal, and Rheumatology*****\$28.95**

Review

FILBIN

Lippincott Williams & Wilkins, 2003, 192 pages,  
ISBN 1405103515

This book follows the format of the Blueprints series, in which each case takes the form of a discussion followed by key points and a series of questions. The pathophysiology volumes would be a good companion to organ-based teaching modules, but the material is neither comprehensive enough nor sufficiently concise to be high yield for intensive boards preparation.

**B-*****Review Questions for Human Pathology*****\$29.95**

Test/1300 q

JONES

CRC Press, 1999, 322 pages, ISBN 1850705992

Features more than 1300 questions with answers and discussions. Many questions are in outdated USMLE format. Step 1-level questions are interspersed with questions at the level of Step 2 and Step 3. A good value for the price.

**B-*****Blueprints Notes & Cases—Pathophysiology:  
Cardiovascular, Endocrine, and Reproduction*****\$28.95**

Review

LEUNG

Lippincott Williams & Wilkins, 2003, 208 pages,  
ISBN 1405103507

This book follows the format of the Blueprints series, in which each case takes the form of a discussion followed by key points and a series of questions. The pathophysiology volumes would be a good companion to organ-based teaching modules, but the material is neither comprehensive enough nor sufficiently concise to be high yield for intensive boards preparation.



A<sup>-</sup>

***Pharmacology Flash Cards***

**\$34.95**

Flash cards

**BRENNER**

Elsevier, 2006, 576 pages, ISBN 1416031863

Flash cards for over 200 of the most commonly tested drugs. Presents name (generic and brand) on front with the basic drug information on the back. Divided and color-coded by class. Comes with a useful compact carrying case. Limited student feedback.

A<sup>-</sup>

***Lippincott's Illustrated Reviews: Pharmacology***

**\$46.95**

Review/125 q

**HOWLAND**

Lippincott Williams & Wilkins, 2005, 559 pages, ISBN 0781741181

An outline format with practice questions and many excellent illustrations and tables. Cross-referenced to other books in the Lippincott's Illustrated Reviews series. Good for the "big picture," and takes an effective pathophysiologic approach. Highly detailed, so use with coursework and review for the USMLE. For the motivated student.

A<sup>-</sup>

***Katzung and Trevor's Pharmacology:***

***Examination and Board Review***

**\$42.95**

Review/1000 q

**TREVOR**

McGraw-Hill, 2004, 640 pages, ISBN 0071422900

A well-organized text in narrative format with concise explanations. Features good charts and tables. Good for drug interactions and toxicities. Offers two practice exams with questions and detailed answers. Includes some low-yield/obscure drugs. The crammable list of "top boards drugs" is especially high yield. Compare with *Lippincott's Illustrated Reviews: Pharmacology*.

B<sup>+</sup>

***Pharmacology for the Boards and Wards***

**\$32.95**

Review/150 q

**AYALA**

Blackwell Science, 2006, 256 pages, ISBN 1405105119

Like other books in the Boards and Wards series, the pharmacology volume is presented primarily in tabular format with bulleted key points. Review questions are in USMLE style. At times can be too dense, but does a great job at focusing on the clinical aspects of the drugs.

**B<sup>+</sup>*****Pharm Cards: A Review for Medical Students*****\$36.95**

Flash cards

JOHANNSEN

Lippincott Williams & Wilkins, 2002, 228 pages,  
ISBN 0781734010

Highlights important features of major drugs and drug classes. Good for class review; also offers a quick, focused review for the USMLE. Lacks pharmacokinetics, but features good charts and diagrams. Well liked by students who enjoy flash card-based review. Bulky to carry around.

**B<sup>+</sup>*****BRS Pharmacology Flash Cards*****\$29.95**

Flash cards

KIM

Lippincott Williams & Wilkins, 2004, 640 pages,  
ISBN 0781747961

Cards focus on facilitating the recall of drugs used for particular diseases rather than describing these drugs in detail. May be useful for those who find *Pharm Cards* overwhelming. Considered by many to be an excellent resource for quick review before the boards.

**B<sup>+</sup>*****Lange Smart Charts: Pharmacology*****\$36.95**

Review

PELLETIER

McGraw-Hill, 2003, 386 pages, ISBN 0071388788

Pharmacology concepts organized into a tabular format. Most useful when used as a secondary source for organization when reviewing material. Limited student feedback.

**B<sup>+</sup>*****Pharm Recall*****\$32.95**

Review

RAMACHANDRAN

Lippincott Williams & Wilkins, 2000, 491 pages,  
ISBN 068330285X

An approach to pharmacology review presented in a question and answer “recall” format. Includes a high-yield drug summary. Good for cramming and memorization.

**B*****Underground Clinical Vignettes: Pharmacology*****\$19.95**

Review

BHUSHAN

Lippincott Williams & Wilkins, 2005, 154 pages,  
ISBN 1405104171

Concise clinical cases illustrating approximately 100 frequently tested pharmacology concepts. Cardinal signs, symptoms, and buzzwords are highlighted. The clinical vignette style is less effective for pharmacology. Use as a supplement to other sources of review.

**B****Pharmacology****\$49.95**

Text

**BRENNER**

Elsevier, 2006, 512 pages, ISBN 1416029842

Well-written text organized similar to other pharmacology books. Presents information in clear and concise manner with mechanisms and clinical examples. New edition has self-assessment questions at the end of each chapter. Provides links to Student Consult Web site. Too lengthy for boards review. Best if used along with course.

**B****Clinical Pharmacology Made Ridiculously Simple****\$22.95**

Review

**OLSON**

MedMaster, 2006, 163 pages, ISBN 094078073

Includes general principles and many drug summary charts. Particularly strong in cardiovascular drugs and antimicrobials; incomplete in other areas. Consists primarily of tables; lacks the humorous illustrations and mnemonics typical of this series. Well organized, but occasionally too detailed. Effective as a chart-based review book but not as a sole study source. Must be supplemented with a more detailed text.

**B****Rapid Review: Pharmacology****\$34.95**

Review/350 q

**PAZDERNICK**

Elsevier, 2005, 352 pages + CD-ROM, ISBN 0323045502

Similar to other books in the Rapid Review series. Figures are sparse but are high yield when included. Provides limited detail on mechanisms of action. Contains two 50-question tests with additional questions on a CD-ROM. Compare with *High-Yield Pharmacology*. Limited student feedback.

**B****PreTest Pharmacology****\$24.95**

Test/500 q

**SHLAFER**

McGraw-Hill, 2004, 480 pages, ISBN 007143688X

New edition represents a significant improvement over previous editions of the book. A good resource to use after other sources of questions have been exhausted.

**B****Case Files: Pharmacology****\$29.95**

Review

**TOY**

McGraw-Hill, 2005, 456 pages, ISBN 0071445730

A clinical case review book consisting of 52 cases along with useful tables. The text may appeal to students who prefer problem-based learning, but some may find it difficult to review pharmacology using a clinical vignette format.

**B-*****High-Yield Pharmacology*****\$25.95**

Review

**CHRIST**

Lippincott Williams & Wilkins, 2003, 138 pages,  
ISBN 0781745128

A pharmacology review presented in an easy-to-follow outline format. Contains no questions or index. Offers a good summary. Best used with a more extensive text.

**B-*****Appleton & Lange's Review of Pharmacology*****\$34.95**

Test/800 q

**KRZANOWSKI**

McGraw-Hill, 2002, 155 pages, ISBN 0071377433

A text that contains ample, up-to-date questions along with a 50-question practice test. Best for students who need additional pharmacology questions for boards review. Answers have no accompanying text or explanations, which may pose a challenge for those who require more detailed information.

**B-*****Instant Pharmacology*****\$70.00**

Text

**SAEB-PARSY**

John Wiley & Sons, 1999, 349 pages, ISBN 0471976393

A text divided into several parts, the first addressing basic mechanisms found in pharmacology. Drugs encountered in this section are summarized in the "Dictionary of Drugs." Concludes with a comprehensive exam. Includes answers but no explanations. Best if used during coursework.

**A****Physiology****\$49.95**

Text

**COSTANZO**

Elsevier, 2006, 512 pages, ISBN 1416023208

Comprehensive coverage of concepts outlined in *BRS Physiology*. Offers excellent diagrams and charts. Each systems-based chapter includes a detailed summary of objectives and a boards-relevant clinical case. Includes access to online interactive extras. Requires time commitment.

**A****BRS Physiology****\$36.95**

Review/400 q

**COSTANZO**

Lippincott Williams & Wilkins, 2003, 337 pages,  
ISBN 0781739195

A clear, concise review of physiology that is both comprehensive and efficient, making for fast, easy reading. Includes great charts and tables. Good practice questions are given along with explanations and a clinically oriented final exam. An excellent review book, but may not be enough for in-depth coursework. Respiratory and acid-base sections are comparatively weak.

**A-****BRS Physiology Cases and Problems****\$36.95**

Review/Many q

**COSTANZO**

Lippincott Williams & Wilkins, 2006, 384 pages,  
ISBN 078176078X

Roughly 50 cases in vignette format with several questions per case. Includes detailed answers with explanations. For the motivated student.

**A-****USMLE Road Map: Physiology****\$19.95**

Review/50 q

**PASLEY**

McGraw-Hill, 2006, 208 pages, ISBN 0071400761

A text in outline format incorporating high-yield illustrations. Provides a concise approach to physiology. Clinical correlations are referenced to the text. Questions build on basic concepts and include detailed explanations. Limited student feedback.

**B+****Deja Review: Physiology****\$22.95**

Review

**LIN**

McGraw-Hill, 2007, 216 pages, ISBN 0071475109

Features questions and answers in a two-column, quiz-yourself format. Similar to Recall series. Provides a sound review in a different format than straight text. Includes very helpful graphics and tables. Limited student feedback.

**B<sup>+</sup>*****High-Yield Acid Base*****\$25.95**

Review

LONGENECKER

Lippincott Williams & Wilkins, 1998, 100 pages,  
ISBN 0683303937

A concise and well-written description of acid-base disorders. Includes chapters discussing differential diagnoses and 12 clinical cases. Introduces a multistep approach to the material. A bookmark with useful factoids is included with the text. No index or questions.

**B<sup>+</sup>*****Appleton & Lange's Review of Physiology*****\$34.95**

Test/700 q

PENNEY

McGraw-Hill, 2003, 278 pages, ISBN 0071377263

Boards-style questions divided into subcategories under physiology. Good if subject-specific questions are desired, but may be too detailed for many students. Some diagrams are used to explain answers. A good way to test your knowledge after coursework.

**B<sup>+</sup>*****Respiratory Physiology: The Essentials*****\$37.95**

Review/100 q

WEST

Lippincott Williams & Wilkins, 2004, 208 pages,  
ISBN 0781751527

Comprehensive coverage of respiratory physiology. Clearly organized with useful charts and diagrams. The new edition includes appendices with more than 100 questions and answers with explanations. Best used as a course supplement.

**B*****Color Atlas of Physiology*****\$39.95**

Review

DESPOPOULOS

Thieme, 2003, 448 pages, ISBN 1588900614

A compact text with more than 150 colorful but complicated diagrams on the right and dense explanatory text on the left. Suffers from some translation problems. Overall, a unique, highly visual approach that is worthy of consideration. Useful as an adjunct to other review books.

**B*****Clinical Physiology Made Ridiculously Simple*****\$19.95**

Review

GOLDBERG

MedMaster, 2004, 152 pages, ISBN 0940780216

Easy reading with many amusing associations. The style does not work for everyone. Not as well illustrated as the rest of the series. Use as a supplement to other review books.

**B*****Guyton and Hall Physiology Review*****\$29.95**

Test/1000 q

**HALL**

Elsevier, 2005, 260 pages, ISBN 072168307X

Over 1000 questions that provide a good review of physiology. Questions are much shorter and not as involved as those on the boards. Best if used as a review resource for areas of weakness in physiology. Limited student feedback.

**B*****Netter's Atlas of Human Physiology*****\$45.95**

Review

**HANSEN**

Icon Learning Systems, 2002, 224 pages, ISBN 1929007019

An organ system-based text with more than 250 of Dr. Netter's classic illustrations. Offers a clear, concise, "big picture" view of physiology. May be too detailed for boards review. Limited student feedback.

**B*****Lange Smart Charts: Physiology*****\$34.95**

Review

**LYN**

McGraw-Hill, 2004, 400 pages, ISBN 0071395075

Major topics in physiology organized into chart form according to body system. Includes mnemonics and definitions of key terms, but lacks detail at times. Suitable as an adjunct to another source. Limited student feedback.

**B*****Review Questions for Physiology*****\$29.95**

Test/700 q

**PASLEY**

CRC Press-Parthenon, 1998, 142 pages, ISBN 1850706018

Few clinical vignette-type questions. Answers are on the same page as the questions, making it easy to move through questions and check answers at the same time.

**B*****Acid-Base, Fluids, and Electrolytes  
Made Ridiculously Simple*****\$18.95**

Review

**PRESTON**

MedMaster, 2002, 156 pages, ISBN 0940780313

Covers major electrolyte disturbances and fluid management issues with which medical students should be familiar. A great reference for the internal medicine clerkship. Provides information beyond the scope of the USMLE, but remains a useful companion for understanding physiology, kidney function, and fluids. Includes scattered diagrams and questions at the end of each chapter that test comprehension more than facts. Some questions involve calculations.

**B*****PreTest Physiology*****\$24.95**

Test/500 q

**RYAN****McGraw-Hill, 2004, 480 pages, ISBN 0071436537**

Questions with detailed, well-written explanations. The new edition offers more USMLE-oriented questions as well as more focused explanations. One of the best of the PreTest series. May be useful for the motivated student following extensive review of other sources. Includes 32 pages of high-yield facts.

**B*****Metabolism at a Glance*****\$36.95**

Review

**SALWAY****Blackwell Science, 2004, 128 pages, ISBN 1405107162**

A concise and impressive review of the biochemical pathways involved in metabolism. Intricate figures depict the interplay between the various reactions. Beyond the scope of the USMLE, but a unique resource for course work.



Commercial preparation courses can be helpful for some students, but such courses are expensive and require significant time commitment. They are usually an effective tool for students who feel overwhelmed by the volume of material they must review in preparation for the boards. Note, too, that the multiweek review courses may be quite intense and may thus leave limited time for independent study. Also note that while some commercial courses are designed for first-time test takers, others focus on students who are repeating the examination. Still other courses focus on IMGs who want to take all three Steps in a limited amount of time. Finally, student experience and satisfaction with review courses are highly variable, and course content and structure can evolve rapidly. We thus suggest that you discuss options with recent graduates of review courses you are considering. Some student opinions can be found in discussion groups on the World Wide Web.

### Falcon Physician Reviews

Established in 2002, Falcon Physician Reviews provides intensive and comprehensive live reviews for students preparing for the USMLE and COMLEX. The seven-week Step 1 reviews are held throughout the year with small class sizes in order to increase student involvement and instructor accessibility. Falcon Physician Reviews uses an active learning system that focuses on comprehension, retention, and application of concepts. Program components include:

- Application-based lecture materials
- Free tutoring
- Over 12,000 USMLE type sample questions
- Clinical vignettes
- USMLE questions integrated into each lecture
- Case histories
- Sample tests

Programs are currently offered in Dallas, Texas and Miami, Florida. The fee is \$3,950. The all-inclusive program tuition fee includes:

- Books and study materials
- Over 325 contact hours
- Hotel accommodations
- Daily full breakfast and lunch
- Ground transportation to and from the airport
- Shuttle service to shopping, movies, and other areas of interest

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 1431 Greenway Drive #800  
 Irving, TX 75038  
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 214.292.8568 Fax  
 info@falconreviews.com  
 URL: www.falconreviews.com

## Kaplan Medical

Kaplan Medical offers a wide range of options for USMLE preparation, including live lectures, center-based study, and online products. All of its courses and products focus on providing the most exam-relevant information available.

**Live Lectures.** Kaplan's IntensePrep™ offers a highly structured, interactive live review led by expert faculty. Designed for medical students with little time to prepare, it includes approximately 15 days of live lectures during which faculty members cover the material students need to know to master the Step 1 exam. IntensePrep students also receive six months of access to Kaplan's online lectures, which offers more than 80 hours of high-yield, audio-streamed lectures. This course features seven volumes of lecture notes and a question book that includes 850 practice questions.

Kaplan also offers live-lecture courses ranging from 6 to 14 weeks with all-inclusive options to stay and study in high-end hotel accommodations, all of which are aimed at students who are repeating the exam as well as students and physicians who seek more time to prepare.

**Center Study.** CenterPrep 30 Visits, Kaplan's center-based lecture course, is designed for medical students seeking flexibility. It is offered at more than 160 Kaplan Centers across the United States and includes 30 visits to one Kaplan Center, where students are given access to over 160 hours of video lecture review. This course also includes seven volumes of lecture notes; a question book that includes 850 practice questions; and a full-length simulated exam with a complete performance analysis and detailed explanations. For those who would like more access to study resources, Kaplan offers CenterPrep, which includes a personalized study plan and three months of access to one Kaplan Center of your choice.

**Online Resources.** Kaplan Medical provides online content and question-based review. WebPrep offers 80 hours of audio-streamed lectures, seven volumes of lecture notes, a full online Step 1 simulated exam, and access to its popular online question bank, Qbank, which contains over 2,150 USMLE-style practice questions with detailed explanations. WebPrep is designed to be the most flexible content and question-based review available.

Kaplan's popular Qbank allows students to customize practice tests by discipline and organ system, receive instant on-screen feedback, and track their cumulative performance. Another Step 1 resource is Kaplan's Integrated Vignettes Qbank, an online clinical case question bank that allows users to practice answering case-based, USMLE-style vignettes that are organized by symptom. Each vignette contains multidisciplinary questions covering different ways the underlying basic science concepts could be tested.

Kaplan's most comprehensive question practice option is Qreview, which contains more than 3,750 questions and provides six months of simultaneous access to both Step 1 Qbank and IV Qbank. Qreview provides students with collective reporting of their results across both Qbanks and also includes an online simulated exam for further USMLE practice. Qbank demos are available at [www.kaplanmedical.com](http://www.kaplanmedical.com).

More information on all of Kaplan's review options can be obtained at (800) 533-8850 or by visiting [www.kaplanmedical.com](http://www.kaplanmedical.com).

## Northwestern Medical Review

Northwestern Medical Review offers live-lecture review courses for both the COMLEX Level I and USMLE Step 1 examinations. Four review plans are available for each exam: NBI 100, a three-day course; NBI 150, a four-day course; NBI 200, a five-day course; and NBI 300, a 10- or 15-day course. All courses are in live-lecture format, and most are taught by the authors of the Northwestern Review Books. In addition to organized lecture notes and books for each subject, courses include Web-based question bank access, audio CDs and a large pool of practice questions and simulated exams. All plans are available in a customized, onsite format for groups of second-year students from individual U.S. medical schools. Additionally, public sites are frequently offered in East Lansing and Detroit, Michigan; Philadelphia, Pennsylvania; St. Louis, Missouri; San Antonio, Texas; Los Angeles, California; Baltimore, Maryland; and Long Island, New York. International sites may also be offered at the request of groups of students and international educational organizations.

Tuition ranges from \$390 for the 3-day to \$1,380 for the 15-day course. Tuition includes all study materials and Web usage services, and it is based on group size, program duration, and early-enrollment discounts. Home-study materials, CBT question-bank access, and DVD materials are also available for purchase independent of the live-lecture plans. Northwestern offers a retake option as well as a liberal cancellation policy.

For more information, contact:

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Lansing, MI 48909-2174  
Phone: (866) MedPass  
Fax: (517) 347-7005  
E-mail: registrar@northwesternmedicalreview.com  
URL: www.northwesternmedicalreview.com

## Postgraduate Medical Review Education (PMRE)

Established in 1976, PMRE offers complete home-study courses for the USMLE Step 1 in the form of audio cassettes and books. Home Study Package A offers live classes on audiotapes and a transcript book with a compilation of handout notes from the professors that you will hear on the cassettes for \$998. Package C offers 15 hours of audio tapes and transcript contains 3,500 keywords, 400 exam strategies, and 150 acronyms for the 7 basic sciences (Biochemistry, Microbiology, Physiology, Pharmacology, Pathology, Anatomy, and Behavioral Science) for \$500. Package E features 9000 questions and answers on 20 hours of audiotape for \$250. PMRE uses professors who write questions for USMLE exams in conjunction with professionally recorded materials. PMRE is recognized by the AMA and The Federation Licensing Medical Examiners, Ft. Worth, Texas. Books are being sold at the UCLA medical book store, Barnes and Noble, and McGill Medical University book store, Montreal, Canada.

For more information, contact:

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Phone: (800) 323-6430  
Fax: (954) 921-2222  
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## The Princeton Review

The Princeton Review offers three flexible preparation options for the USMLE Step 1: the USMLE Online Course, the USMLE Classroom Course, and the USMLE Online Workout. In selected cities, The Princeton Review also offers a more intensive preparation course for IMGs.

**USMLE Online Course.** The USMLE Online Course offers comprehensive, self-paced preparation that includes the following:

- Seventy-five hours of online review, including lessons, vignettes, and drills
- Three full-length diagnostic tests with detailed score reports
- Seven comprehensive review manuals consisting of more than 1500 pages
- Seven minitests to gauge students' knowledge in each subject
- Twenty-four-hour e-mail support from Princeton Review Online instructors
- Three months of online access

**USMLE Online Workout.** The USMLE Online Workout offers the following:

- Two thousand USMLE-style questions presented in the CBT format
- Three full-length diagnostic exams
- Seven minitests covering Anatomy, Behavioral Science, Biochemistry, Microbiology and Immunology, Pathology, Pharmacology, and Physiology
- More than 40 subject-specific drills
- A high-yield slide review for Anatomy and Pathology
- Complete explanations of all questions and answers
- Three months of access

**USMLE Classroom Courses.** The USMLE Classroom Courses offer the following:

- 156 hours of classroom instruction from a medical resident
- 75 hours of online review, including lessons, vignettes, and drills
- 3 full-length diagnostic tests with detailed score reports
- 7 comprehensive review manuals – 1500+ pages
- 7 mini-tests to gauge your knowledge in each subject

More information can be found on The Princeton Review's Web site at [www.princetonreview.com](http://www.princetonreview.com).

## Doctor Youel's Prep, Inc.

Doctor Youel's Prep, Inc., has specialized in medical board preparation for nearly 30 years. The company provides DVDs, audiotapes, videotapes, a CD (PowerPrep™, Quick Start™), a book (7 Steps to Board Success), live lectures, and tutorials for small groups as well as for individuals (TutorialPrep™). All DVDs, videotapes, audiotapes, live lectures, and tutorials are correlated with a three-book set of Prep Notes© consisting of two textbooks, *Youel's Jewels I*© and *Youel's Jewels II*© (984 pages); and *Case Studies*, a question-and-answer book (1854 questions, answers, and explanations).

The Home Study program includes: Comprehensive VideoPrep™ with books (56 hours of live lectures by the systems), FasTrac™ program (CD + books), and books. The 3-book set consists of: *Youel's Jewels I and II*™ and *Case Studies*™. The 2 textbooks contain 984 pages and the Case Studies book has 1854 questions, answers, and explanations.

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[www.youelsprep.com](http://www.youelsprep.com)

# APPENDIX

## Abbreviations and Symbols

Abbreviation	Meaning	Abbreviation	Meaning
1°	primary	ARDS	adult respiratory distress syndrome
2°	secondary	Arg	arginine
3°	tertiary	ASA	acetylsalicylic acid
AA	amino acid	ASD	atrial septal defect
AAV	adeno-associated virus	ASO	antistreptolysin O
Ab	antibody	Asp	aspartic acid
ABP	androgen-binding protein	AST	aspartate transaminase
Ac-CoA	acetylcoenzyme A	AT	angiotensin
ACD	anemia of chronic disease	ATP	adenosine triphosphate
ACE	angiotensin-converting enzyme	ATPase	adenosine triphosphatase
ACh	acetylcholine	AV	atrioventricular
AChE	acetylcholinesterase	AVM	arteriovenous malformation
ACL	anterior cruciate ligament	AZT	azidothymidine
ACTH	adrenocorticotrophic hormone	BAL	British anti-Lewisite [dimercaprol]
ADA	adenosine deaminase, Americans with Disabilities Act	BMI	body-mass index
ADH	antidiuretic hormone	BMR	basal metabolic rate
ADHD	attention-deficit hyperactivity disorder	BP	blood pressure
ADP	adenosine diphosphate	BPG	bis-phosphoglycerate
AFP	$\alpha$ -fetoprotein	BPH	benign prostatic hyperplasia
Ag	antigen	BUN	blood urea nitrogen
AICA	anterior inferior cerebellar artery	CAD	coronary artery disease
AIDS	acquired immunodeficiency syndrome	cAMP	cyclic adenosine monophosphate
ALA	aminolevulinic acid	C-ANCA	cytoplasmic antineutrophil cytoplasmic antibody
ALL	acute lymphocytic leukemia	CBSSA	Comprehensive Basic Science Self-Assessment
ALS	amyotrophic lateral sclerosis	CBT	computer-based testing
ALT	alanine transaminase	CCK	cholecystokinin
AML	acute myelocytic leukemia	CCl <sub>4</sub>	carbon tetrachloride
AMP	adenosine monophosphate	CCS	computer-based case simulation
ANA	antinuclear antibody	CCT	cortical collecting tubule
ANCA	antineutrophil cytoplasmic antibody	CD	cluster of differentiation
ANOVA	analysis of variance	CDP	cytidine diphosphate
ANP	atrial natriuretic peptide	CE	cholesterol ester
ANS	autonomic nervous system	CEA	carcinoembryonic antigen
AOA	American Osteopathic Association	CETP	cholesterol-ester transfer protein
AP	action potential	CF	cystic fibrosis
APC	antigen-presenting cell	CFU	colony-forming unit
APRT	adenine phosphoribosyltransferase	CFX	circumflex [artery]
APSAC	anistreplase	cGMP	cyclic guanosine monophosphate
AR	autosomal recessive	ChAT	choline acetyltransferase
ARC	Appalachian Regional Commission	CHF	congestive heart failure

Abbreviation	Meaning	Abbreviation	Meaning
CIN	candidate identification number, cervical intraepithelial neoplasia	DO	doctor of osteopathy
CJD	Creutzfeldt-Jakob disease	DOPA	dihydroxyphenylalanine (methyl dopa)
CK-MB	creatine kinase, MB fraction	2,3-DPG	2,3-diphosphoglycerate
CL	clearance	DPM	doctor of podiatric medicine
CLL	chronic lymphocytic leukemia	DPPC	dipalmitoyl phosphatidylcholine
CM	chylomicron	DS	double stranded
CML	chronic myeloid leukemia	dsDNA	double-stranded deoxyribonucleic acid
CMT	Computerized Mastery Test	dsRNA	double-stranded ribonucleic acid
CMV	cytomegalovirus	dTMP	thymidine-5'-phosphate
CN	cranial nerve	DTR	deep tendon reflex
CNS	central nervous system	DTs	delirium tremens
CO	cardiac output	dUMP	deoxyuridine monophosphate
CoA	coenzyme A	DVT	deep venous thrombosis
COGME	Council on Graduate Medical Education	EBV	Epstein-Barr virus
COMLEX	Comprehensive Osteopathic Medical Licensing Examination	EC <sub>50</sub>	median effective concentration
COMT	catechol-O-methyltransferase	ECF	extracellular fluid
COPD	chronic obstructive pulmonary disease	ECFMG	Educational Commission for Foreign Medical Graduates
COX	cyclooxygenase	ECG	electrocardiogram
C <sub>p</sub>	plasma concentration	ECT	electroconvulsive therapy
CPAP	continuous positive airway pressure	ECV	effective circulating volume
CPK	creatine phosphokinase	ED <sub>50</sub>	median effective dose
CRH	corticotropin-releasing hormone	EDTA	ethylenediamine tetra-acetic acid
CSA	Clinical Skills Assessment	EDV	end-diastolic volume
CSF	cerebrospinal fluid, colony-stimulating factor	EEG	electroencephalogram
CT	computed tomography	EF	ejection fraction, elongation factor
CVA	cardiovascular accident, costovertebral angle	ELISA	enzyme-linked immunosorbent assay
Cx	complication	EM	electron micrograph, electron microscopic, electron microscopy
Cys	cysteine	EMB	eosin-methylene blue
d4T	didehydrodeoxythymidine [stavudine]	EOM	extraocular muscle
DAF	decay-accelerating factor	epi	epinephrine
DAG	diacylglycerol	EPO	erythropoietin
dATP	deoxyadenosine triphosphate	EPS	extrapyramidal system
ddC	dideoxycytidine	ER	endoplasmic reticulum
ddI	didanosine	ERAS	Electronic Residency Application Service
DES	diethylstilbestrol	ERCP	endoscopic retrograde cholangiopancreatography
DHAP	dihydroxyacetone phosphate	ERP	effective refractory period
DHB	dihydrobiopterin	ERPF	effective renal plasma flow
DHEA	dehydroepiandrosterone	ERV	expiratory reserve volume
DHF	dihydrofolic acid	ESR	erythrocyte sedimentation rate
DHPG	dihydroxy-2-propoxymethyl guanine	ESV	end-systolic volume
DHS	Department of Homeland Security	EtOH	ethyl alcohol
DHT	dihydrotestosterone	FAD	oxidized flavin adenine dinucleotide
DI	diabetes insipidus	FADH <sub>2</sub>	reduced flavin adenine dinucleotide
DIC	disseminated intravascular coagulation	FAP	familial adenomatous polyposis
DIP	distal interphalangeal [joint]	5f-dUMP	5-fluorodeoxyuridine monophosphate
DIT	diiodotyrosine	FE <sub>Na</sub>	excreted fraction of filtered sodium
DKA	diabetic ketoacidosis	FEV <sub>1</sub>	forced expiratory volume in 1 second
DNA	deoxyribonucleic acid	FF	filtration fraction
2,4-DNP	2,4-dinitrophenol	FFA	free fatty acid
		FGF	fibroblast growth factor

Abbreviation	Meaning	Abbreviation	Meaning
FLEX	Federation Licensing Examination	HHS	[Department of] Health and Human Services
f-met	formylmethionine	HHV	human herpesvirus
FMG	foreign medical graduate	5-HIAA	5-hydroxyindoleacetic acid
FMN	flavin mononucleotide	His	histidine
FRC	functional residual capacity	HIV	human immunodeficiency virus
FSH	follicle-stimulating hormone	HLA	human leukocyte antigen
FSMB	Federation of State Medical Boards	HMG-CoA	hydroxymethylglutaryl-coenzyme A
FTA-ABS	fluorescent treponemal antibody—absorbed	HMP	hexose monophosphate
5-FU	5-fluorouracil	HMWK	high-molecular-weight kininogen
FVC	forced vital capacity	HNPPC	hereditary nonpolyposis colorectal cancer
G3P	glucose-3-phosphate	hnRNA	heterogeneous nuclear ribonucleic acid
G6P	glucose-6-phosphate	HPA	hypothalamic-pituitary-adrenal [axis]
G6PD	glucose-6-phosphate dehydrogenase	HPSA	Health Professional Shortage Area
GABA	$\gamma$ -aminobutyric acid	HPV	human papillomavirus
GBM	glomerular basement membrane	HR	heart rate
G-CSF	granulocyte colony-stimulating factor	HSV	herpes simplex virus
GFAP	glial fibrillary acid protein	HSV-1	herpes simplex virus 1
GFR	glomerular filtration rate	HSV-2	herpes simplex virus 2
GGT	$\gamma$ -glutamyl transpeptidase	5-HT	5-hydroxytryptamine (serotonin)
GH	growth hormone	HTLV	human T-cell leukemia virus
GI	gastrointestinal	HUS	hemolytic-uremic syndrome
GIP	gastric inhibitory peptide	IBD	inflammatory bowel disease
GIST	gastrointestinal stromal tumor	IC	inspiratory capacity
Glu	glutamic acid	ICA	internal carotid artery
GM-CSF	granulocyte-macrophage colony-stimulating factor	ICF	intracellular fluid
GMP	guanosine monophosphate	ICP	intracranial pressure
GN	glomerulonephritis	ID <sub>50</sub>	median infectious dose
GnRH	gonadotropin-releasing hormone	IDDM	insulin-dependent diabetes mellitus
GPe	globus pallidus externa	IDL	intermediate-density lipoprotein
GPi	globus pallidus interna	I/E	inspiratory/expiratory [ratio]
GRP	gastrin-releasing peptide	IF	immunofluorescence
GSH	reduced glutathione	IFN	interferon
GSSG	oxidized glutathione	Ig	immunoglobulin
GTP	guanosine triphosphate	IHSS	idiopathic hypertrophic subaortic stenosis
GU	genitourinary	IL	interleukin
HAART	highly active antiretroviral therapy	Ile	isoleucine
HAV	hepatitis A virus	IMA	inferior mesenteric artery
Hb	hemoglobin	IMED	International Medical Education Directory
HBcAb	hepatitis B core antibody	IMG	international medical graduate
HBcAg	hepatitis B core antigen	IMP	inosine monophosphate
HBeAb	hepatitis B early antibody	IND	Investigational New Drug
HBeAg	hepatitis B early antigen	INH	isonicotine hydrazine [isoniazid]
HBsAb	hepatitis B surface antibody	IP <sub>3</sub>	inositol triphosphate
HBsAg	hepatitis B surface antigen	IPV	inactivated polio vaccine
HBV	hepatitis B virus	IRV	inspiratory reserve volume
hCG	human chorionic gonadotropin	ITP	idiopathic thrombocytopenic purpura
HCV	hepatitis C virus	IV	intravenous
HDL	high-density lipoprotein	IVC	inferior vena cava
HDV	hepatitis D virus	JG	juxtaglomerular [cells]
HEV	hepatitis E virus	JGA	juxtaglomerular apparatus
HGPRTase	hypoxanthine-guanine phosphoribosyltransferase		



Abbreviation	Meaning	Abbreviation	Meaning
KSHV	Kaposi's sarcoma-associated herpesvirus	MTP	metatarsophalangeal [joint]
LA	left atrial	MUA/P	Medically Underserved Area and Population
LAD	left anterior descending [artery]	MVO <sub>2</sub>	myocardial oxygen consumption
LCA	left coronary artery	NAD <sup>+</sup>	oxidized nicotinamide adenine dinucleotide
LCAT	lecithin-cholesterol acyltransferase	NADH	reduced nicotinamide adenine dinucleotide
LCL	lateral collateral ligament	NADP <sup>+</sup>	oxidized nicotinamide adenine dinucleotide phosphate
LCME	Liaison Committee on Medical Education	NADPH	reduced nicotinamide adenine dinucleotide phosphate
LCV	lymphocytic choriomeningitis virus	NBME	National Board of Medical Examiners
LDH	lactate dehydrogenase	NBOME	National Board of Osteopathic Medical Examiners
LDL	low-density lipoprotein	NBPME	National Board of Podiatric Medical Examiners
LES	lower esophageal sphincter	NDA	New Drug Application
Leu	leucine	NE	norepinephrine
LFA-1	leukocyte function-associated antigen 1	NF	neurofibromatosis
LFT	liver function test	NH <sub>3</sub>	ammonia
LGN	lateral geniculate nucleus	NIDDM	non-insulin-dependent diabetes mellitus
LH	luteinizing hormone	NK	natural killer [cells]
LLQ	left lower quadrant	NPV	negative predictive value
LM	light microscopy	NSAID	nonsteroidal anti-inflammatory drug
LMN	lower motor neuron	OAA	oxaloacetic acid
LSE	Libman-Sacks endocarditis	OCD	obsessive-compulsive disorder
LT	leukotriene	OCP	oral contraceptive pill
LV	left ventricle, left ventricular	OMT	osteopathic manipulative technique
Lys	lysine	OPV	oral polio vaccine
MAC	membrane attack complex	OR	odds ratio
MAO	monoamine oxidase	PA	posteroanterior
MAOI	monoamine oxidase inhibitor	PABA	para-aminobenzoic acid
MAP	mean arterial pressure	PAH	para-aminohippuric acid
MCA	middle cerebral artery	PALS	periarterial lymphatic sheath
MCHC	mean corpuscular hemoglobin concentration	PAN	polyarteritis nodosa
MCL	medial collateral ligament	P-ANCA	perinuclear antineutrophil cytoplasmic antibody
MCP	metacarpophalangeal [joint]	PAS	periodic acid Schiff
MCV	mean corpuscular volume	PC	pyruvate carboxylase
MEN	multiple endocrine neoplasia	PCL	posterior cruciate ligament
MEOS	microsomal ethanol oxidizing system	PCP	phencyclidine hydrochloride, <i>Pneumocystis carinii</i> pneumonia
Met	methionine	PCR	polymerase chain reaction
MGN	medial geniculate nucleus	PCWP	pulmonary capillary wedge pressure
MHC	major histocompatibility complex	PD	posterior descending [artery]
MHPSA	Mental Health Professional Shortage Area	PDA	patent ductus arteriosus
MI	myocardial infarction	PDE	phosphodiesterase
MIT	monoiodotyrosine	PDH	pyruvate dehydrogenase
MLF	medial longitudinal fasciculus	PE	pulmonary embolism
MMR	measles, mumps, rubella [vaccine]	PEP	phosphoenolpyruvate
6-MP	6-mercaptopurine	PFK	phosphofructokinase
MPO	myeloperoxidase	PFT	pulmonary function test
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine	PG	prostaglandin
MRI	magnetic resonance imaging		
mRNA	messenger ribonucleic acid		
MRSA	methicillin-resistant <i>S. aureus</i>		
MS	multiple sclerosis		
MSH	melanocyte-stimulating hormone		

Abbreviation	Meaning	Abbreviation	Meaning
Phe	phenylalanine	SER	smooth endoplasmic reticulum
PICA	posterior inferior cerebellar artery	SEVIS	Student and Exchange Visitor Information System
PID	pelvic inflammatory disease	SEVP	Student and Exchange Visitor Program
PIP	proximal interphalangeal [joint]	SGOT	serum glutamic oxaloacetic transaminase
PIP <sub>2</sub>	phosphatidylinositol 4,5-bisphosphate	SGPT	serum glutamic pyruvate transaminase
PK	pyruvate kinase	SHBG	sex hormone-binding globulin
PKD	polycystic kidney disease	SIADH	syndrome of inappropriate antidiuretic hormone
PKU	phenylketonuria	SLE	systemic lupus erythematosus
PML	progressive multifocal leukoencephalopathy	SLL	small lymphocytic lymphoma
PMN	polymorphonuclear [leukocyte]	SMA	superior mesenteric artery
PNET	primitive neuroectodermal tumor	SMX	sulfamethoxazole
PNH	paroxysmal nocturnal hemoglobinuria	SNc	substantia nigra compacta
PNS	peripheral nervous system	snRMP	small nuclear ribonucleoprotein
POMC	pro-opiomelanocortin	SOD	superoxide dismutase
PPRF	paramedian pontine reticular formation	SR	sarcoplasmic reticulum
PPV	positive predictive value	SRP	sponsoring residency program
PRPP	phosphoribosylpyrophosphate	SRS-A	slow-reacting substance of anaphylaxis
PSA	prostate-specific antigen	SS	single stranded
PSS	progressive systemic sclerosis	ssDNA	single-stranded deoxyribonucleic acid
PT	prothrombin time	SSPE	subacute sclerosing panencephalitis
PTH	parathyroid hormone	SSRI	selective serotonin reuptake inhibitor
PTHrP	parathyroid hormone-related protein	ssRNA	single-stranded ribonucleic acid
PTSD	post-traumatic stress disorder	STD	sexually transmitted disease
PTT	partial thromboplastin time	STN	subthalamic nucleus
PV	plasma volume	SV	sinus venosus, stroke volume
RA	rheumatoid arthritis	SVC	superior vena cava
RBC	red blood cell	SVT	supraventricular tachycardia
RBF	renal blood flow	t <sub>1/2</sub>	half-life
RCA	right coronary artery	T <sub>3</sub>	triiodothyronine
RDS	respiratory distress syndrome	T <sub>4</sub>	thyroxine
RDW	red-cell distribution width	TB	tuberculosis
REM	rapid eye movement	TBG	thyroxine-binding globulin
RER	rough endoplasmic reticulum	TBW	total body water
RNA	ribonucleic acid	3TC	dideoxythiacytidine [lamivudine]
RPF	renal plasma flow	TCA	tricarboxylic acid [cycle], tricyclic antidepressant
RPR	rapid plasma reagin	Tc cell	cytotoxic T cell
RR	relative risk, respiratory rate	TCR	T-cell receptor
rRNA	ribosomal ribonucleic acid	TD <sub>50</sub>	median toxic dose
RS	Reed-Sternberg [cells]	TFT	thyroid function test
RSV	respiratory syncytial virus	TG	triglyceride
RUQ	right upper quadrant	TGF	transforming growth factor
RV	right ventricle, right ventricular, residual volume	THB	tetrahydrobiopterin
RVH	right ventricular hypertrophy	Th cell	helper T cell
SA	sinoatrial, subarachnoid	THF	tetrahydrofolate
SAM	S-adenosylmethionine	Thr	threonine
SARS	severe acute respiratory syndrome	TIBC	total iron-binding capacity
SC	subcutaneous	TLC	total lung capacity
SCID	severe combined immunodeficiency disease	TMP-SMX	trimethoprim-sulfamethoxazole
SD	standard deviation, subdural		
SEM	standard error of the mean		
SERM	selective estrogen receptor modulator		

Abbreviation	Meaning	Abbreviation	Meaning
TN	trigeminal neuralgia	USIA	United States Information Agency
TNF	tumor necrosis factor	USMLE	United States Medical Licensing Examination
TNM	tumor, node, metastases [staging]	UTI	urinary tract infection
TOEFL	Test of English as a Foreign Language	UV	ultraviolet
tPA	tissue plasminogen activator	VA	ventral anterior, Veterans Administration
TPP	thiamine pyrophosphate	Val	valine
TPR	total peripheral resistance	VC	vital capacity
TRAP	tartrate-resistant acid phosphatase	V <sub>d</sub>	volume of distribution
TRH	thyrotropin-releasing hormone	VDRL	Venereal Disease Research Laboratory
tRNA	transfer ribonucleic acid	VEGF	vascular endothelial growth factor
Trp	tryptophan	VF	ventricular fibrillation
TSH	thyroid-stimulating hormone	VIP	vasoactive intestinal peptide
TSI	thyroid-stimulating immunoglobulin	VIPoma	vasoactive intestinal polypeptide-secreting tumor
TSS	toxic shock syndrome	VLDL	very low density lipoprotein
TSST	toxic shock syndrome toxin	VMA	vanillylmandelic acid
TTP	thrombotic thrombocytopenic purpura	VPL	ventral posterior nucleus, lateral
TV	tidal volume	VPM	ventral posterior nucleus, medial
TXA	thromboxane	VPN	ventral posterior nucleus
UA	urinalysis	V/Q	ventilation/perfusion [ratio]
UCV	Underground Clinical Vignettes	VSD	ventricular septal defect
UDP	uridine diphosphate	VZV	varicella-zoster virus
UMN	upper motor neuron	WBC	white blood cell
URI	upper respiratory infection	XR	X-linked recessive
USDA	United States Department of Agriculture		

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Ali Kemal Ozturk, MD



Deepak Rao

### Vikas Bhushan, MD

Vikas is an author, editor, entrepreneur, and roaming teleradiologist who divides his days between Los Angeles, Maui, and balmy remote locales with abundant bandwidth. In 1992 he conceived and authored the original *First Aid for the USMLE Step 1*, and in 1998 he originated and coauthored the *Underground Clinical Vignettes* series. His entrepreneurial adventures include a successful software company; a medical publishing enterprise (S2S); an e-learning company (Medsn); and, most recently, an ER teleradiology venture (24/7 Radiology). His eclectic interests include medical informatics, independent film, humanism, Urdu poetry, world music, South Asian diasporic culture, and avoiding a day job. He has also coproduced a music documentary on qawwali; coproduced and edited *Shabash 2.0: The Hip Guide to All Things South Asian in North America* (available at [www.artwallah.org/shabash](http://www.artwallah.org/shabash)); and is now completing a CD/book project on Sufi poetry translated into four languages. Vikas completed a bachelor's degree in biochemistry from the University of California, Berkeley; an MD with thesis from the University of California, San Francisco; and a radiology residency from the University of California, Los Angeles.

### Tao T. Le, MD, MHS

Tao has led the last 8 consecutive revisions of *First Aid for the USMLE Step 1* and is a well-recognized figure in medical education. As senior editor, he expanded *First Aid* into a global educational series. In addition, he is the founder of the *USMLERx* online test bank series as well as a cofounder of the *Underground Clinical Vignettes* series. As a medical student, he was editor-in-chief of the University of California, San Francisco *Synapse*, a university newspaper with a weekly circulation of 9000. Tao earned his medical degree from the University of California, San Francisco, in 1996 and completed his residency training in internal medicine at Yale University and fellowship training at Johns Hopkins University. At Yale, he was a regular guest lecturer on the USMLE review courses and an adviser to the Yale University School of Medicine curriculum committee. Tao subsequently went on to cofound Medsn and served as its Chief Medical Officer. He is currently conducting research in asthma education at the University of Louisville.

### Ali Kemal Ozturk, MD

Ali Kemal Ozturk is currently an intern at the Yale-New Haven Hospital Department of Neurosurgery. He is originally from New Orleans, Louisiana, and went to college at Johns Hopkins University, where he studied biology and graduated with a BA in 2001. His research interests include genetics of vascular malformations of the brain. When he finds time from the hospital, he enjoys spending time at his home in New Haven with his fiancée, Christina.

### Deepak Rao

Deepak is currently a fifth-year MD-PhD student at the Yale University School of Medicine, and this is his third year on the *First Aid* team. Born and raised in Philadelphia, Deepak developed an interest in basic science research as an undergraduate at Harvard University, where he received an AB degree in 2001. He participated in a one-year pre-IRTA training fellowship at the NIH studying muscular dystrophy before enrolling in the Medical Scientist Training Program at Yale. He has worked as a private tutor for several years and has also participated on the education and curriculum committee at Yale. Deepak is currently working towards a PhD in immunology studying immune responses generated against the vasculature of solid organ transplants. He looks forward to returning to medical school after completing his PhD.

## ABOUT THE AUTHORS